Regenerative Medicine and Cell & Gene Therapy in Japan: Information Materials for CDMO and Related Companies

This document is a compilation of non-confidential slide decks from companies belonging to the FIRM CDMO sub-committee. If you have inquiries regarding specific companies, please refer to their respective websites or contact FIRM at info@firm.or.jp.

Feb. 2024

CDMO sub-committee
Forum of Innovative Regenerative Medicine (FIRM)

CDMO and Related Companies in Regenerative Medicine and Cell & Gene Therapy in Japan

Organization	Manufacturing (※1)		Culture media/Raw materials	Storage	Transport	Exami-nation	License & regulatory service (※2)	Page
	Gene therapy	Cell therapy						
AGC Biologics	レ	レ				レ	レ	3–33
Cyto-Facto	レ	レ						34–67
J-TEC		レ		レ		レ		68–75
Kyokuto Pharmaceutical Industrial			レ					76–78
MEDINET		レ		レ		レ	レ	79–94
MITSUI-SOKO				レ	レ			95
REPROCELL		レ	レ			レ	レ	96–141
ROHTO Pharmaceuticals	レ	レ						142–143
SRL						レ	レ	144–158
Takara Bio	レ	レ	レ	レ		レ	レ	159–170
Teijin		レ		レ		レ	レ	171–195

※1 Gene therapy includes treatments used in vivo gene therapy and oncolytic virus, but it does not include ex vivo gene therapy like CAR-T. On the other hand, cell therapy encompasses ex vivo gene therapy like CAR-T, as well as other forms of cell therapy such as MSC (Mesenchymal Stem Cell) and tissue engineering products.

※2 The items marked with "レ" below include the following:

- A company has expertise in working with regulatory authorities, even in cases where there is no approval history with them.
- A company provides pharmaceutical regulatory assistance services.

002

AGC Biologics

Global CDMO Services for Biologics and Cell & Gene Therapies

AGC Biologics Company Introduction

Our Purpose

Cardiovascular Diseases

Pediatric Metachromatic Leukodystrophy

Febrile Neutropenia

Arthritis, Spondylitis

COVID-19

Refractory Acute Myeloid Leukemia

Homocystinuria

Systemic Lupus Erythematosus

*Our purpose is to **bring hope to life** by enabling life-changing therapies for patients around the globe, creating a healthier and happier tomorrow.*

Soft-Tissue Sarcoma

Anemia

Treatment of Solid Tumors

Diabetes

Rheumatoid Arthritis

Fibrosis and Inflammatory Disease

Crohn's Disease

Malignant lymphoma

Pulmonary Arterial Hypertension (PAH)

AGC Biologics

Our Core Values

KNOWLEDGE – We possess strong scientific and technical expertise

TRUST – We create positive experiences that our customers can rely on

QUALITY – We strive for excellence in our people, products and services

INGENUITY – We find creative solutions to difficult challenges

ACCOUNTABILITY – We follow through on our commitments

TEAMWORK – We put the success of the team above our own personal goals

AGC Biologics

Our Mission

To work side by side with our customers in order to **improve patients' lives** by bringing new biopharmaceuticals to market.


Mammalian


Microbial


pDNA


Viral Vector


Cell Therapy


mRNA

AGC Biologics

Our Services — *from Pre-Clinical to Commercial*

Tech Transfer

Our collaborative approach ensures an efficient & successful transfer process

Analytical Development

Our methods ensure your product's identity, safety, purity, and potency

Process Validation

We help deliver a robust and cost-effective supply for commercial approval

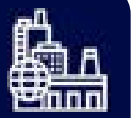
Process Development

We can apply existing processes or develop new, innovative processes

Formulation Development

We provide innovative solutions to the specific challenges posed by your individual protein or therapy

cGMP Manufacturing

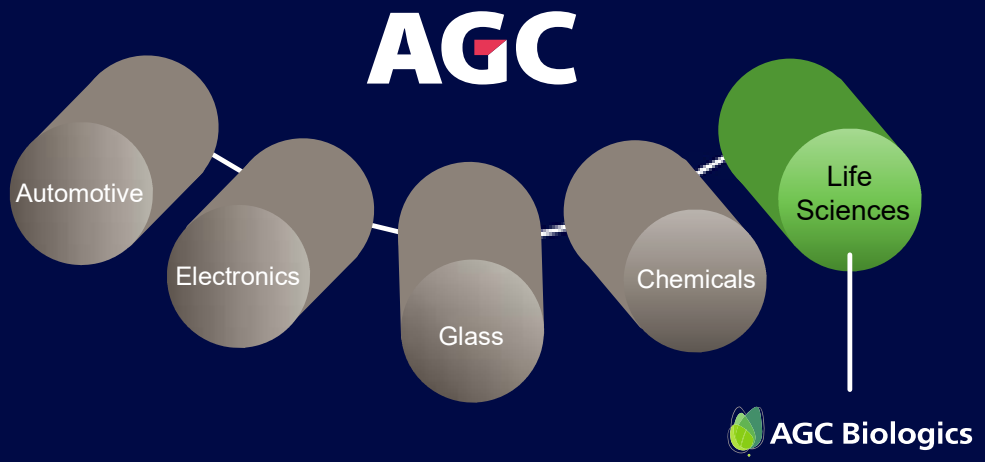


We offer capacity and technological ingenuity you can rely on at every stage, from clinical to commercial

AGC Biologics

AGC Biologics is Part of AGC, Inc.

- Founded in 1907
- Headquarters in Tokyo, Japan
- Net FY sales: 2,036 B Yen (~14.1 B USD)
- 57,000+ employees globally
- Strategic businesses driving revenue and future growth:



Benefits for AGC Biologics Customers

Financial stability and backing of a global organization

Long-term vision and strategic plan for AGC Biologics

Access to capital to expand global capabilities and capacity

Our History

1907 — **Asahi Glass Co. (AGC) Founded**

Pictured above:
AGC Inc. HQ located in Tokyo, Japan

1973 — **AGC Inc, Life Science Team established**

1993 — **Biomeva Founded**

2001 — **CMC Biologics Founded**

2007 — **CMC Biologics Acquired ICOS**

2008 — **AGC Inc, Chiba facility started CDMO business**

2016 — **AGC Inc. Acquired Biomeva**

2017 — **AGC Inc. Acquired CMC Biologics**

2018 — **AGC Biologics Formed (Biomeva + CMC + AGC Biosciences)**

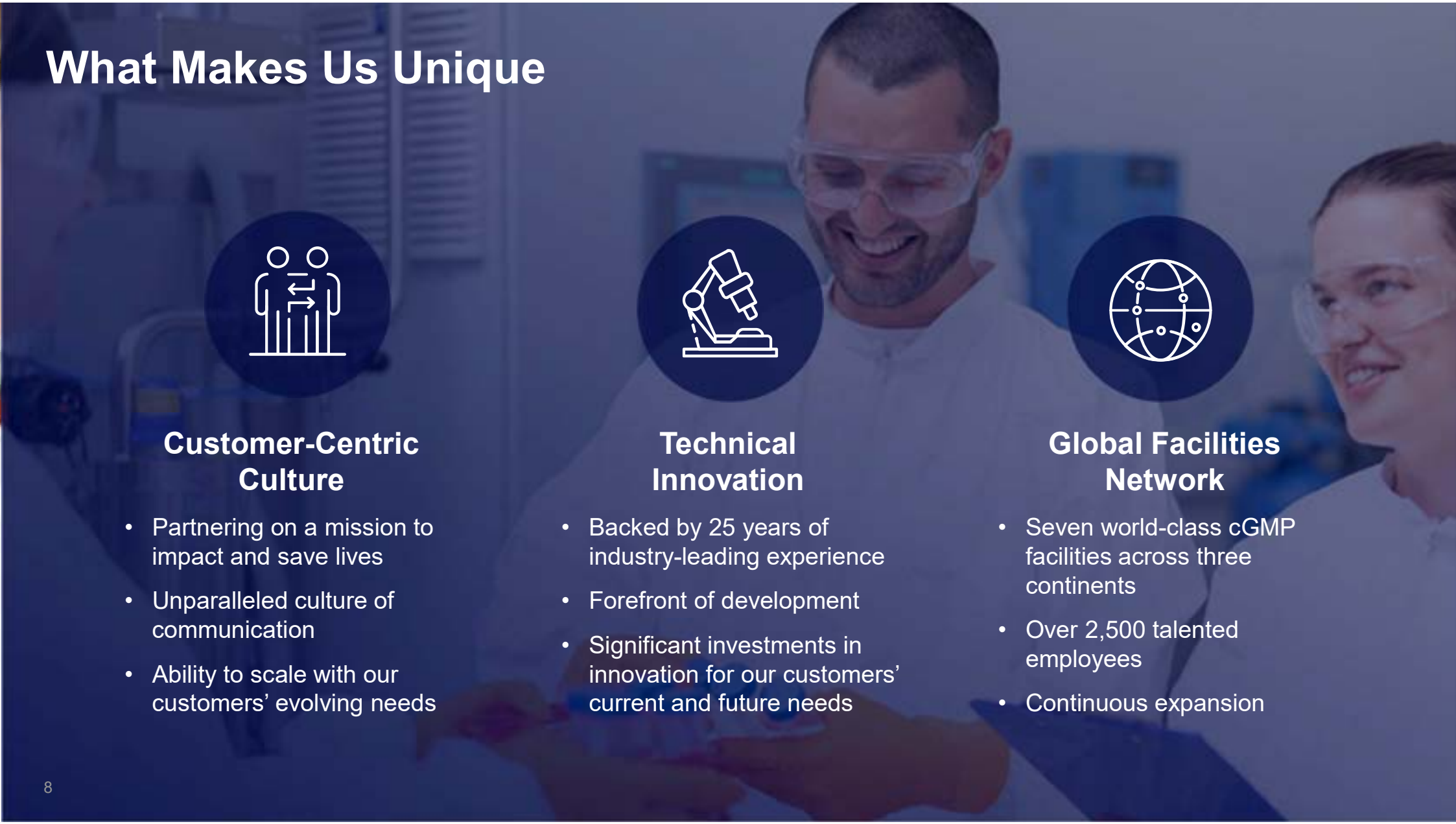
Pictured above:
AGC Biologics HQ located in Bothell, WA

2020 — **Acquired Facility in Boulder, CO and MolMed in Milan, Italy**

2021 — **Acquired Facility in Longmont, CO**

Pictured above:
Main entrance of Longmont Campus

What Makes Us Unique



Customer-Centric Culture

- Partnering on a mission to impact and save lives
- Unparalleled culture of communication
- Ability to scale with our customers' evolving needs

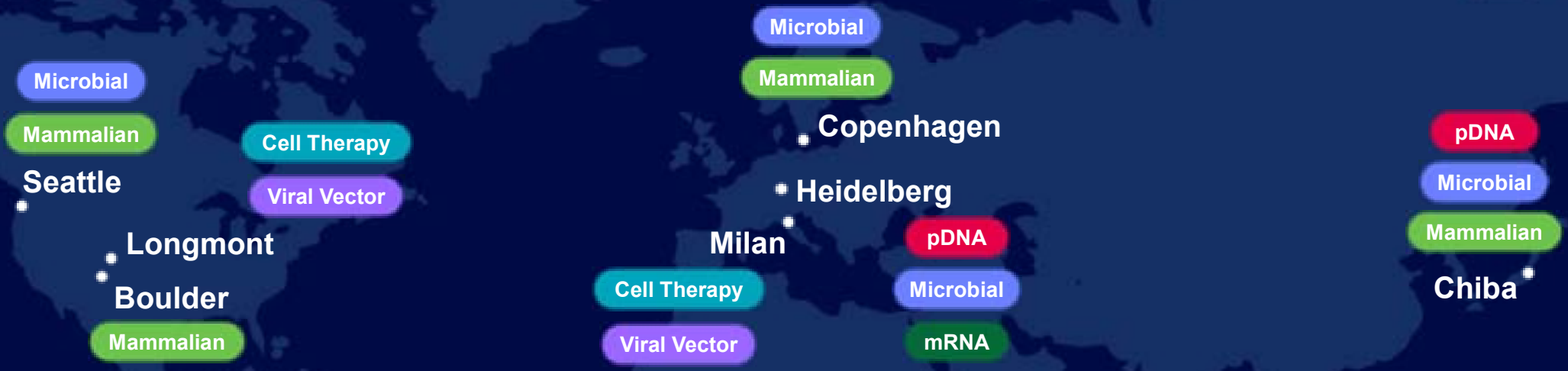
Technical Innovation

- Backed by 25 years of industry-leading experience
- Forefront of development
- Significant investments in innovation for our customers' current and future needs

Global Facilities Network

- Seven world-class cGMP facilities across three continents
- Over 2,500 talented employees
- Continuous expansion

Our Global Network



7	2,500+	175+
FACILITIES	EMPLOYEES	CUSTOMERS SERVED

AGC Biologics

Our Global Network

Seattle

Seattle

Washington, USA

Mammalian

Microbial

Regulatory Approvals: FDA, PMDA FMA Acquired

- Mammalian manufacturing scale from 100 L to 12,000 L, including Bioreactor 6Pack™ technology
- Upstream, downstream and analytical development
- Center of Excellence for formulation
- Fed-batch and perfusion manufacturing processes
- Expansion completed on the installation of 24,000 L added mammalian capacity and a 1,500 L microbial production facility

AGC Biologics

Our Global Network

Longmont

Longmont
Colorado, USA

Cell Therapy

Viral Vector

Regulatory Approvals: FDA Registered

- 100+ GMP commercialization batches produced without failure
- Analytical and process development for viral vector and cell therapy
- Multi-product viral vector manufacturing and fill / finish (AAV, LVV, RVV)
- Adherent: 24 L / 48 L cell factories, 200 L fixed-bed bioreactor (iCELLis500)
- Suspension: bioreactors ranging 50 L, 200 L, 500 L, 2,000 L
- iCELLis500 bioreactors ranging 200 L, 500 L, 2,000 L
- Multiple new cell therapy processing suites
- Automated fill and finish for viral vectors in early 2024

AGC Biologics

Our Global Network

Boulder

Boulder

Mammalian

Colorado, USA

Regulatory Approvals: FDA Registered

- State-of-the-art large-scale commercial mammalian manufacturing, featuring 2 x 20,000 L vessels (17,000 working volume)
- Designed for high titer DSP processes (up to 10 g/l)
- Large scale volume + high titers = tremendous cost savings
- Ability to expand by two to four 20,000 L vessels

AGC Biologics

Our Global Network

Copenhagen
Denmark

Mammalian

Microbial

Regulatory Approvals: FDA, EMA, HC, PMDA, ANVISA

- Mammalian manufacturing scale from 100 L to 12,000 L, including the Bioreactor 6Pack™ technology
- Three independent mammalian lines with fed-batch and perfusion capabilities
- Microbial manufacturing at 2 x 1,500 L
- Upstream, downstream and analytical development
- New facility adding 8 x 2,000 L single-use bioreactors coming online early 2024

Copenhagen

AGC Biologics

Our Global Network

Heidelberg
Germany

Microbial pDNA mRNA

Regulatory Approvals: FDA, EMA, PMDA FMA Acquired

- Center of Excellence for plasmid DNA, with commercial manufacturing experience
- Offering pDNA supply in all grades and quantities
- mRNA supply in various quantities (R&D / GMP grade)
- Microbial manufacturing scale from 100 L to 1,000 L
- Upstream, downstream and analytical development
- Freedom-to-Operate and RNAse free processes

Heidelberg

AGC Biologics

Our Global Network

Milan

Italy

Cell Therapy

Viral Vector

Regulatory Approvals: EMA, TFDA

- 25+ years of industry-leading expertise and 3 commercially approved products
- Cell therapy and viral vector clinical and commercial capabilities with large GMP capacity
- AAV / LVV / RVV manufacturing and Fill / Finish
- Adherent: 24 L / 48 L cell factories, 200 - 500 L fixed-bed bioreactor (iCELLis500)
- Suspension: 50 L, 200 L and 1,000 L bioreactors
- Cell therapy: 10+ suites performing open and closed processes for both autologous and allogeneic products
- Processes and capabilities for virtually any cell type, $CD34^{+}$HSC, T-Cells, NK Cells, hMSCs and more.
- 160+ in-house analytical tests ensures fast turnaround

AGC Biologics

Our Global Network

Chiba
Japan

Regulatory Approvals: PMDA, MFDS

Mammalian

Microbial

pDNA

- Microbial manufacturing scale up to 3,000 L
- Mammalian manufacturing scale from 500 L to 2,000 L
- Upstream, downstream and analytical development
- Only CDMO in Japan with microbial and mammalian capabilities backed by a global resources network
- pDNA development up to 20 L, stainless steel fermenter
- High-Quality and GMP plasmid manufacturing scale from 100 L to 150 L, stainless steel fermenters

Chiba

AGC Biologics

Seven Sites, One Quality System

Environment, Health & Safety (EHS) is a Top Priority

Regulatory requirements are consistently monitored to ensure compliance.

Established processes help identify potential EHS hazards related to our operations.

EHS Management System ensures a strong focus on ongoing improvement projects.

Process controls in place reduce potential of negative EHS impact by day-to-day operations.

Formal evaluations assess potential EHS impact by new projects and other changes.

Continuous efforts in sustainability development help ensure a bright future for our planet.

Gold Sustainability Rating (CPH)

14001:2015 Environmental (CPH, HDB, SEA)

45001:2018 Health & Safety (CPH, SEA)

50001:2018 Energy (CPH)

WA State, U.S. Safety & Health (SEA)

AGC Biologics

Current Programs & Track Record

AGC Biologics

Experienced Leadership

Patricio Massera
Chief Executive Officer

Kasper Møller, Ph.D.
Chief Technical Officer & Exec. VP, EU & Japan Regions

Tomoko Miyagawa
Executive VP, Corporate Development

JB Agnus
Chief Business Officer

Luis Velez
Executive VP, USA Region

Greg Shelton
Executive VP, People & Culture, General Counsel

Carrie Mygatt
Executive VP, Finance

Akira Nakamura
Senior VP, Corporate & Strategic Planning

Wendy Laderach
Senior VP, Corporate Quality

Andrea Porchia
General Manager, Copenhagen

Dieter Kramer
General Manager, Heidelberg

Jun Takami
General Manager, Chiba

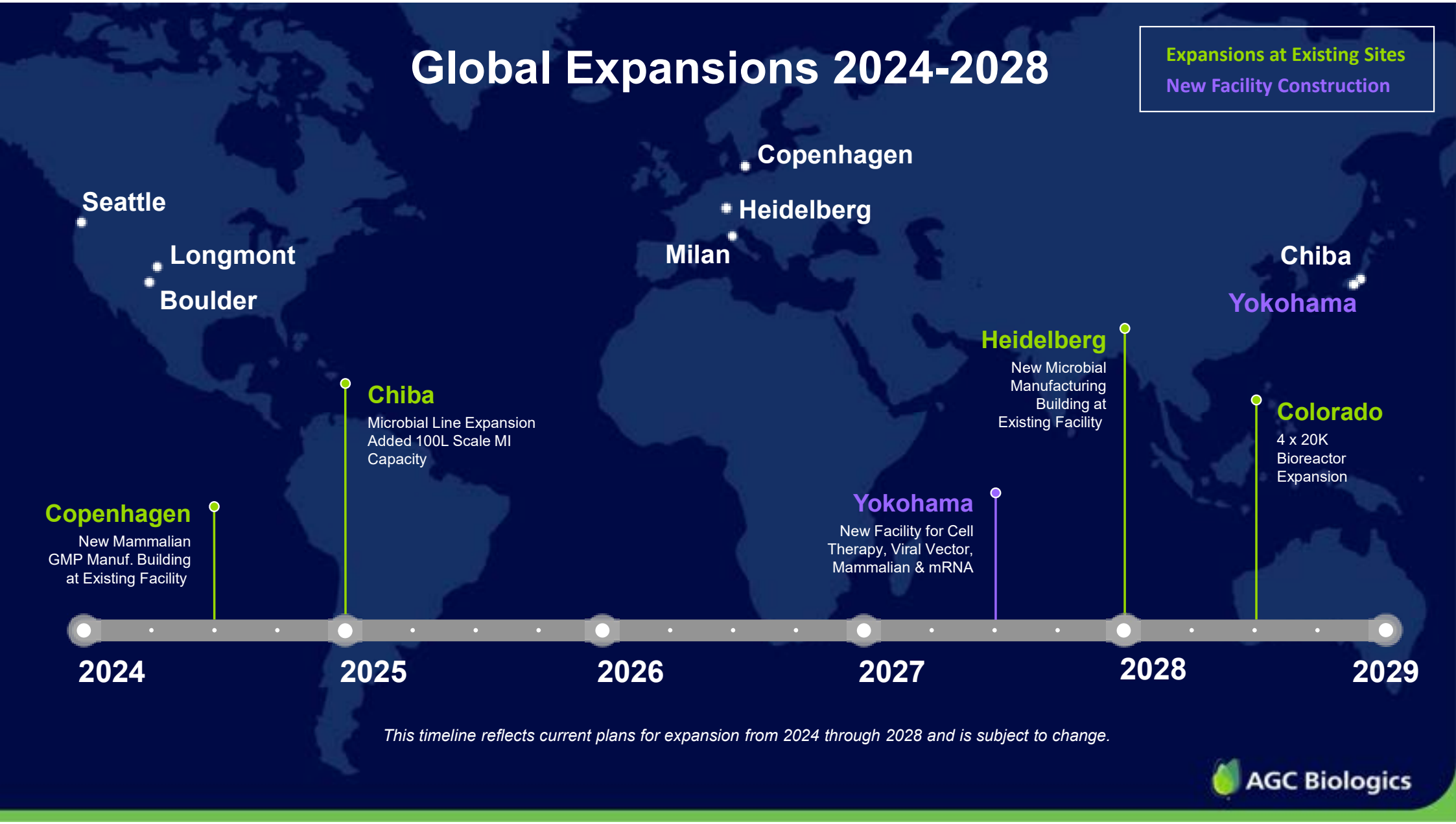
Luca Alberici
General Manager, Milan

Whitney Sandberg
General Manager, Colorado

Mike Tranmer
General Manager, Seattle

Global Expansions 2024-2028

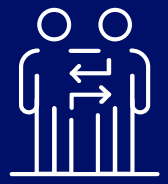
Expansions at Existing Sites
New Facility Construction



This timeline reflects current plans for expansion from 2024 through 2028 and is subject to change.

AGC Biologics

A Partnership You Can Rely On



Customer-Centric Culture

We work side-by-side with you — collaborating, problem solving and being great partners to each other.

Technical Innovation

We are driven by flexible thinking, continuous innovation and technical creativity.

Global Facilities Network

Our globally aligned network of sites in the U.S., Europe and Asia provides a consistent and seamless experience.

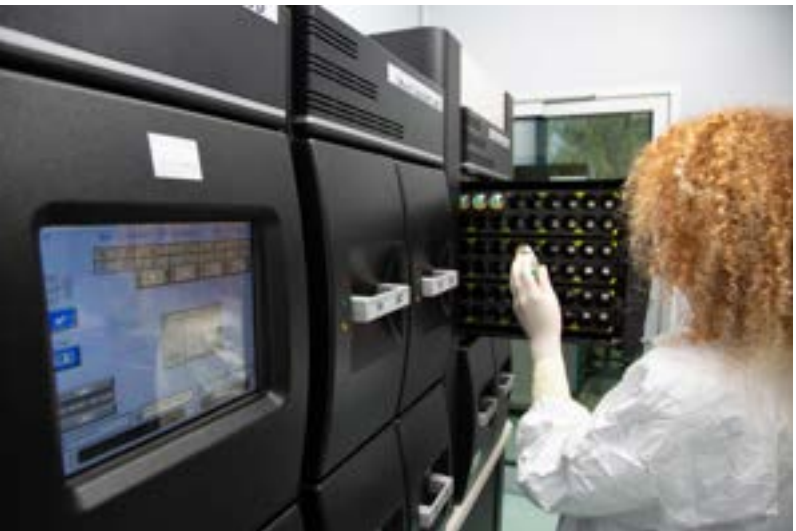
AGC Biologics


AGC Biologics
Thank You
Learn more at agcbio.com

AGC Biologics

BravoAAV™ by AGC Biologics

Standing on 25 years of industry experience, AGC Biologics' scientist have developed the BravoAAV™ platform Process for efficient, fast and reproducible clinical and commercial manufacturing of several AAV serotypes.



AGC's BravoAAV™ platform includes **standardized production and purification** protocols that allow to swap the transgene while keeping the process and analytics constant for retained as well as secreted AAV serotypes'. The BravoAAV™ platform includes ready-to-use, high yield adhesion and suspension **GMP cell lines** as well as helper plasmid that is GMP quality. In addition, pre-implemented and pre-qualified **process and capsid-specific platform methods** shorten the development timeline.

AGC Biologics' BravoAAV™ platform is available for production at different scales in **suspension** (50 L, 200 L, 500 L, 1,000 L and 2,000 L) and **adhesion** (200 L and 500 L).

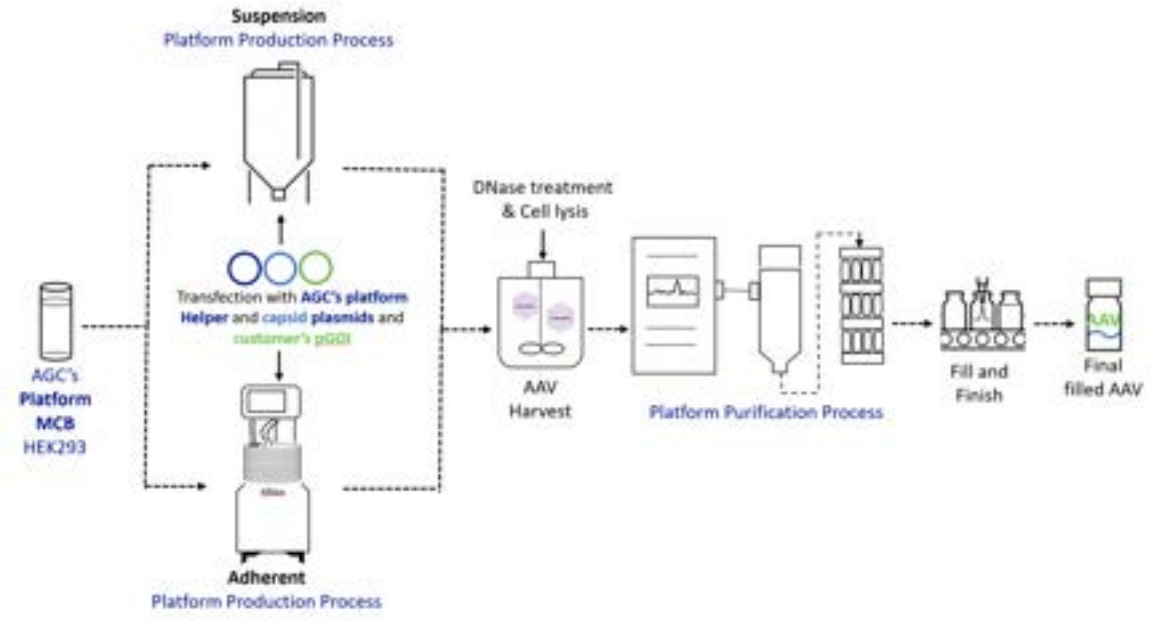
Analytical Methods

Unique to each product
(product specific)

Platform to specific capsid
(serotype specific)

Platform across all AAV
(serotype agnostic)

- Infectious Viral Titer
- GOI sequencing
- Transgene function
- Vector genome by PCR
- V particles by ELISA
- Infectivity
- HPLC full/empty
- Residual HCP
- Residual benzonase
- Residual hc DNA
- Residual E1A DNA
- Residual total DNA
- Residual pDNA
- Residual BSA
- Endotoxin
- Sterility
- In vitro Adv
- rcAAV
- Mycoplasma
- pH/osmo/VP/aggr



Advantages of AGC Biologics' BravoAAV™ Platform

Analytics

- 160+ analytical tests available in house, including potency testing
- 95% of the QC testing panel performed in house

Efficiency

- Platform plasmids for several serotypes and MCB available
- Standardized process allows for template documentation and simplifies the BoM

Reproducibility

- Standardized Process and analytics for several serotypes result in regulatory synergies easing the path to commercialization

Furthermore, AGC Biologics Customers benefit from a global network of manufacturing facilities that provide integrated solutions for plasmid, LVV, RVV and cell therapy manufacturing.

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AGC Biologics

Cell Therapy Capabilities

AGC Biologics brings technical expertise to develop and optimize every aspect of cell therapy. Our services range from production of plasmid DNA necessary for the transfection of producing cells to engineering of cells through the use of produced viral vectors. Our technical know-how allows us to bring small-scale process to scalable industrial manufacturing, ensuring process robustness and commercial viability.

AGC Biologics has the experience to develop and manufacture diverse cell therapies including CD34+ hematopoietic stem cells, **autologous and allogenic** T-cells, and NK cells. Our cell therapy capabilities cover numerous technologies, ranging from closed to open systems at different scales depending on client needs. Our quality systems, facility layout, as well as regulatory qualification, enables us to serve **both clinical and commercial demands**. We perform more than 160 analytical tests in-house to help bring your product to market as fast as possible. With experience manufacturing three commercial products, we are a CDMO that brought a product to the market (Zalmoxis), and understand the procedures and complexities of each step in that process.

Tech Transfer & Development

- Knowledge transfer from client to AGC Biologics
- Feasibility studies for new processes with new reagents and materials
- Transfer of client process at different development stages from R&D scale to cGMP grade
- Optimization studies to improve process performance
- Verification studies to validate the production process
- Comparability studies
- Analytical development for potency and client specific assays
- Qualification of analytical methods before transfer into QC
- Implementation and optimization of automated assays

Analytical Methods Development
Performed In-house

- **Drug Substance**
  - **Potency:** Viability
  - **Safety:** Mycoplasma PCR
  - **Identity:** Immunophenotype
- **Drug Product**
  - Potency:
    - Transgene functional assay
    - Viability
    - Immunophenotype
  - Safety:
    - Endotoxin
    - RCL Molecular assay
    - Microbiological control of cell suspension
  - Identity:
    - Vector identity/integrity

cGMP Manufacturing & Quality Control

- Release, IPC, characterization and stability testing
- Analytical method transfer
- Method validation in accordance with relevant guidelines
- Stability studies management (scheduling, testing, documentation and statistical analysis to support shelf life definition)
- Characterization studies management
- Outsourcing testing management

Quality Assurance

- Raw materials release
- Support with regards to regulatory submissions (IND, IMPD, BLA, MAA)
- Integrated quality systems incorporating US, European, and ICH cGMP requirements
- Comprehensive Quality Agreements
- Regulatory compliance and validation expertise
- History of successful client audits and regulatory inspections
- EU cGMP Certification

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AGC Biologics

ProntoLVV™ by AGC Biologics

Standing on 25 years of industry experience, AGC Biologics' scientist have developed the ProntoLVV™ platform process for efficient, fast and reproducible clinical and commercial manufacturing of LVV. Together with the **standardized production and purification process**, the ProntoLVV platform includes ready-to-use, high yield adhesion and suspension **GMP cell lines** and third generation **packaging plasmids available off the shelf** in several quality grades. In addition, **pre-implemented and pre-qualified platform methods** for several final formulation media shorten the development timeline. Furthermore, AGC's ProntoLVV platform includes **prequalified scale-down models** simplifying the path to PPQ.

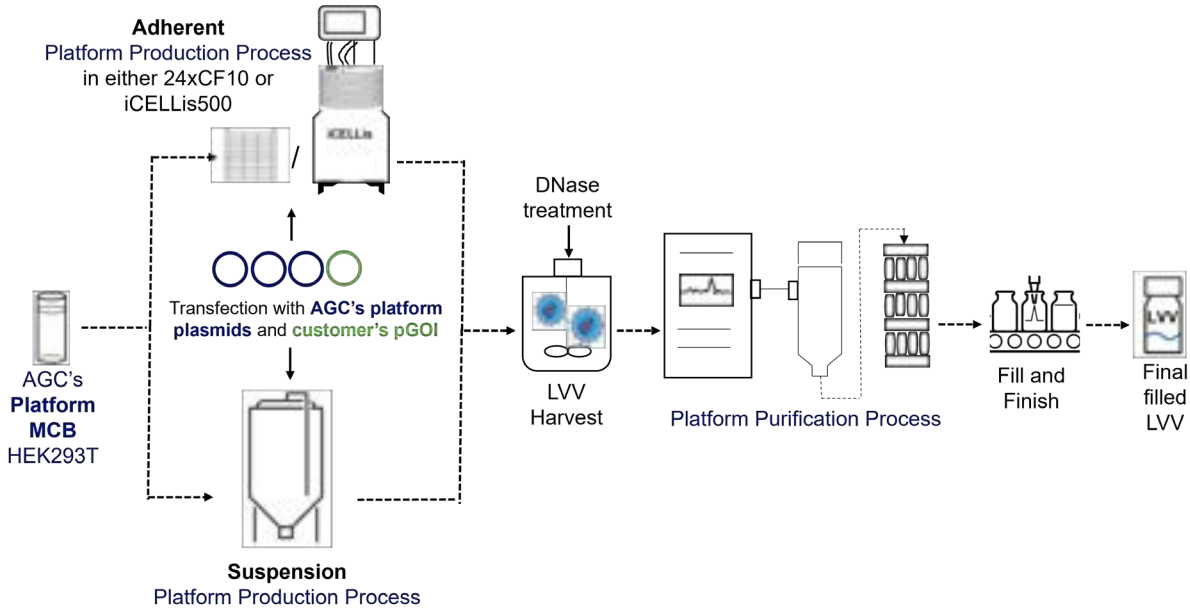
AGC Biologics' ProntoLVV platform is available for production at different scales in **adhesion** (48 L, 200 L and 500 L) and **suspension** (50 L, 200 L, 1000 L, 2000 L).

Analytical Methods

Unique to each product
(product specific)

Platform across all LVV

- Infectious Viral Titer
- GOI sequencing
- Transgene function
- Physical Viral Titer
- Infectivity
- Residual HCP
- Residual benzonase
- Residual LTA DNA
- Residual E1A DNA
- Residual total DNA
- Residual pDNA
- Residual BSA
- Endotoxin
- Sterility
- In vitro Adv
- rcLVV
- Mycoplasma
- pH/osmo/VP/aggr



Advantages of AGC Biologics' ProntoLVV™ Platform

Analytics

- 160+ analytical tests available in house, including potency testing
- 95% of the QC testing panel performed in house

Efficiency

- Off-the-shelf plasmids & MCB
- Standardized process allows for template documentation and simplifies the BoM
- Pre-qualified scale down model simplifies the path to PPQ

Reproducibility

- Reproducible Process proven across more than 40 different transgenes results in regulatory synergies easing the path to commercialization

Furthermore, AGC Biologics customers benefit from a global network of manufacturing facilities that provide integrated solutions for plasmid and cell therapy manufacturing.

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AGC Biologics

Viral Vector Capabilities

AGC Biologics brings technical expertise to develop and optimize every aspect of viral vector gene therapy. Our services range from production of plasmid DNA necessary for the transfection of producing cells to the manipulation and engineering of cells through the use of produced viral vectors. Our technical know-how allows us to bring small-scale process to scalable industrial manufacturing, ensuring process robustness and commercial viability.

AGC Biologics has the experience to develop and manufacture **lenti, retro, and adeno-associated viral vectors**. Our ready-to-use platform capabilities are built on Cell Factories (up to 48 L) and Bioreactor (up to 200 L) using adherent process, designed entirely in-house. Our quality systems, GMP manufacturing scale, as well as regulatory qualification, allow us to meet **both clinical and commercial demand**. Moreover, our scale down capabilities provide flexible and cost-effective solutions for process development and pre-clinical studies. We perform **more than 160 analytical tests in-house** to help bring your product to market as fast as possible. With experience manufacturing two commercial products, we are a CDMO that brought a product to the market (Zalmoxis), and understand the procedures and complexities of each step in that process.

Tech Transfer & Process Development

- Knowledge transfer from client to AGC Biologics
- Feasibility studies for new processes with new reagents and materials
- Ready-to-use Lenti viral vector manufacturing platforms with off-the-shelf materials
- Transfer of client processes at different development stages from R&D scale to cGMP
- Small-scale experiments for production of research and non-clinical batches
- Small-scale run to certify quality of reagents
- Optimization studies to improve process
- Pilot run to set & define the production methods
- LPC & characterization studies
- Comparability studies
- Analytical development for potency & client specific assays
- Qualification of product specific analytical methods before final transfer to QC
- Implement & optimize automated assays

Upstream Process Development

- Flexible scale of production
  - Cell factories ≤ 48 L
  - Bioreactor ≤ 200 L
- Single-use technologies
- Extensive experience of developing in-house and optimizing client processes
- Production scale
  - Petri dishes
  - iCellis 500 system
  - Cell factory
  - iCellis Nano system

Downstream Process Development

- **Separation Chromatography Techniques**
  - Ion exchange
  - Affinity
  - Size exclusion
  - Ligands
- **Tangential Flow Filtration**
  - Ultrafiltration
  - Diafiltration

Analytical Methods Development Performed In-House

- **Potency Assay**
  - Infectious Viral Titer
  - Infectivity
  - Physical Viral Titer
  - Transgene function
- **Identity & Chemical/Physical Characteristic**
  - Vector
  - pH
  - Osmolality
- **Purity**
  - Residual BSA/HCP/BENZONASE
  - Lentiviral Proteins
  - Residual LTA protein
  - Residual VSV-G/LTA/E1A and Total DNA
- **Microbiological Control and Safety**
  - Endotoxin
  - Cultural RCL
  - Sterility

cGMP Manufacturing & Quality Control

- In-house platform in cell factories ≤ 48L
- Release, IPC, characterization & stability testing
- Analytical method transfer
- Method validation in accordance with guidelines
- Stability studies management (scheduling, testing, documentation & statistical analysis)
- Characterization studies management
- Outsourcing testing management
- Raw materials release
- Fill & finish and in-house QC analytics

Quality Assurance

- Support with regards to regulatory submissions Integrated quality systems incorporating US, European, and ICH cGMP requirements
- Comprehensive quality agreements
- Regulatory compliance and validation expertise
- History of successful client audits and regulatory inspections
- EU cGMP certification

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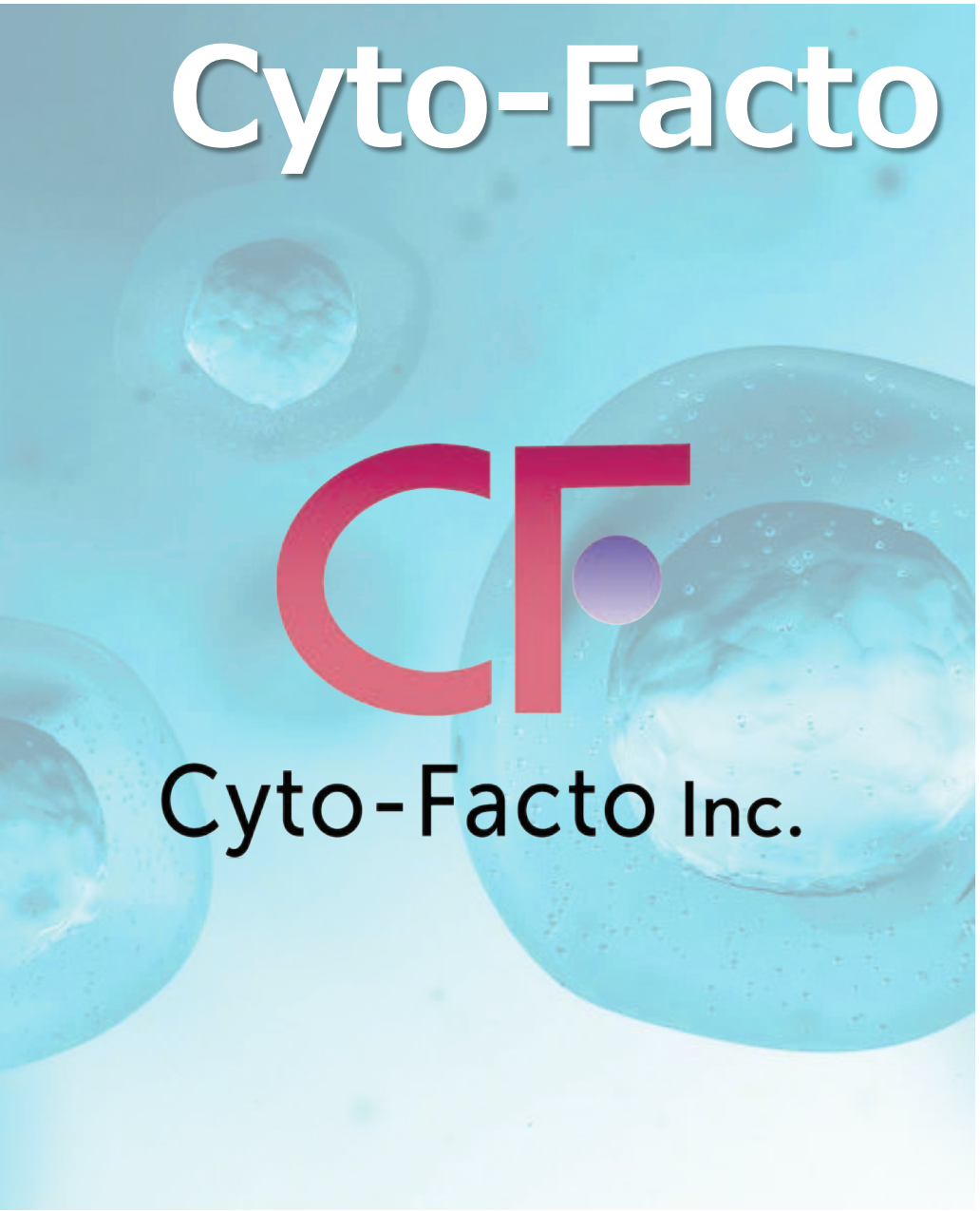
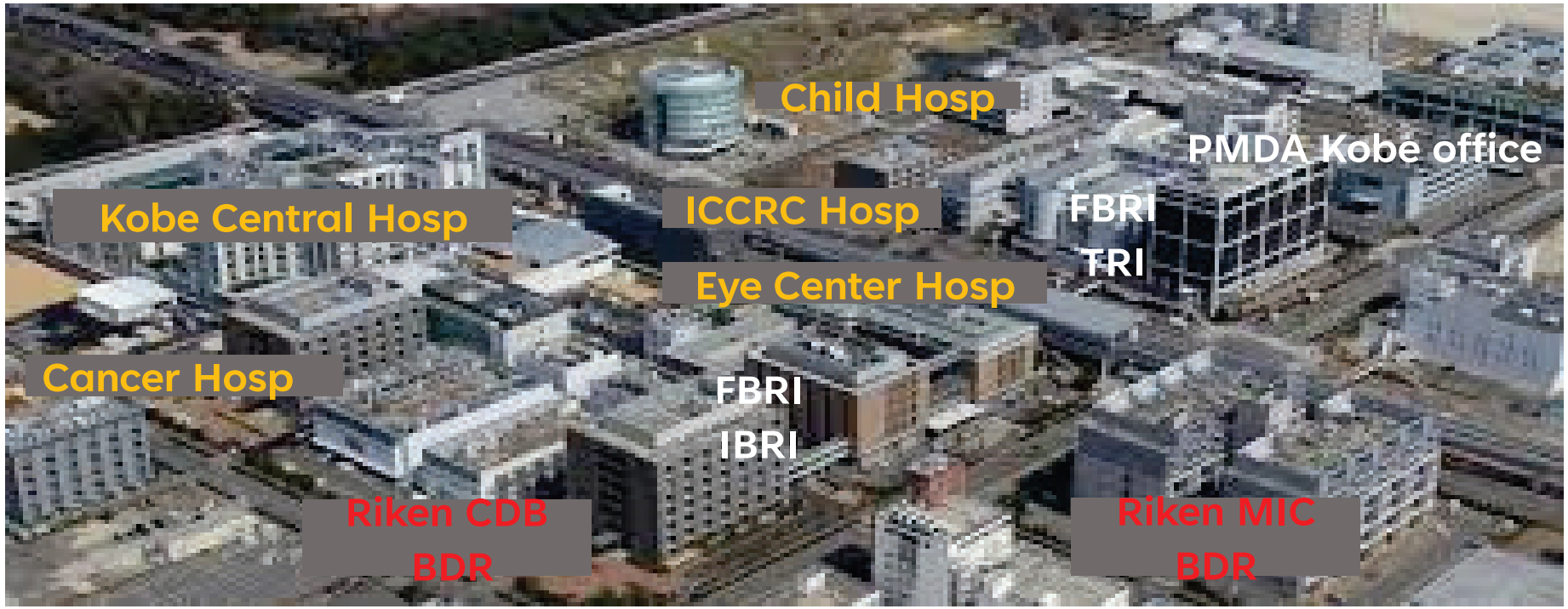


Introduction of Cyto-Facto

2023 Dec.

Cyto-Facto Inc. is a spinoff company

from Foundation for Biomedical Research and Innovation (FBRI)
that aims to support Kobe BioMedical Innovation Cluster project



Kobe BioMedical Innovation Cluster in 2023

2 Riken basic research centers

Translational Institution FBRI

5 universities and collages

5 Hospitals with 1600 beds

PMDA branch office

360 Biomedical companies

FBRI organization chart

Until 2023 March

Tasuku Honjo

Foundation for Biomedical Research and Innovation

Atsuhiko Kawamoto

Medical Innovation Center

Translational research and data center for clinical study

Tadaaki Hanatani

Pro-cluster Center

Foster medical cluster in Kobe and international networking

Shin Kawamata

Center for Cell Therapy

Est 2015

Ext 2023

Regulatory science for cell therapy and cell manufacturing

Toshio Kitamura

Research Center

Research for aging, immune therapy and regenerative medicine

FBRI RDC　until March 2023

Clinical manufacturing CDMO

PM

CDMO

MSC　iPSC-NK

Commercial manufacturing CMO

CMO

CAR T

FBRI RDC FTE 105

research/inspection

New CAR T design

CQA for MSC

CQA for iPSC

Software for cell manufacturing control

Spin off company Cyto-Facto after April 2023

Clinical manufacturing CDMO

PM

CDMO

Commercial manufacturing CMO

CMO

Cyto-Facto Inc.

MSC iPSC-NK

Software for cell manufacturing control

CAR T

FTE 85

CEO Kawamata

research/inspection

Kobe Univ,
Prof Kawamata
FTE 5

New CAR T design

CQA for MSC

CQA for iPSC

MAIN SERVICES

Specialized in manufacturing cell and gene products

- research、process development and sales of products
- CMO/CDMO service
- analytical service and QC testing
- consultation, organizing seminar, training course

Cell manufacturing facilities of Cyto-Facto Inc.

Kobe Sannomiya

Kobe Central Hospital

Cyto-Facto Inc.

CPC for CAR T

CPC Eye Center 600 m²

storage

storage

MEDICAL CENTER

CPC at IBRI 402

QC at IBRI 403

700 m

Preclinical testing

CPC for MSC, iPSC

CPC at KCMI 1200 m²

Cyto-Facto Inc.

SUPER COMPUTER

2 km

Kobe Air port

Introduction of Cell Processing Center

PIC/S GMP compliance manufacturing facility
That allows international shipment
Shipping record to Australia

Introduction of Cell Processing Center

Cell manufacturing facilities of Cyto-Facto Inc.

Kobe Sannomiya

Kobe Central Hospital

Cyto-Facto Inc.

CPC for CAR T

CPC
Eye Center
600 m²

storage

storage

MEDICAL CENTER

CPC
at IBRI
402

QC
at IBRI
403

700 m

Preclinical testing

CPC for MSC, iPSC

CPC
at KCMI
1200 m²

Cyto-Facto Inc.

SUPER COMPUTER

2 km

Kobe Air port

CPC facility in KCMI 5F

FUJIFILM Value from Innovation　Healios

SINFONIA

5CPCs
Central QC Room
Material Storage Room

Total 1,200㎡

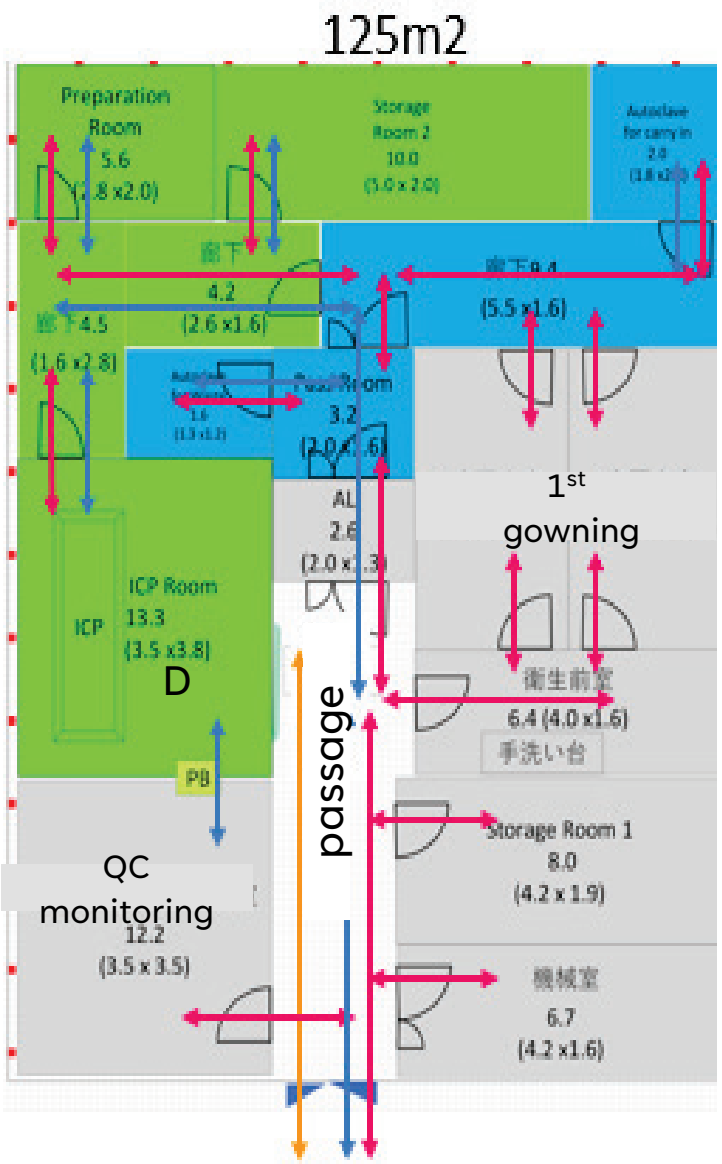
・Clinical Trial of Autologous MSC

・Clinical Trial of eNK derived from iPSC

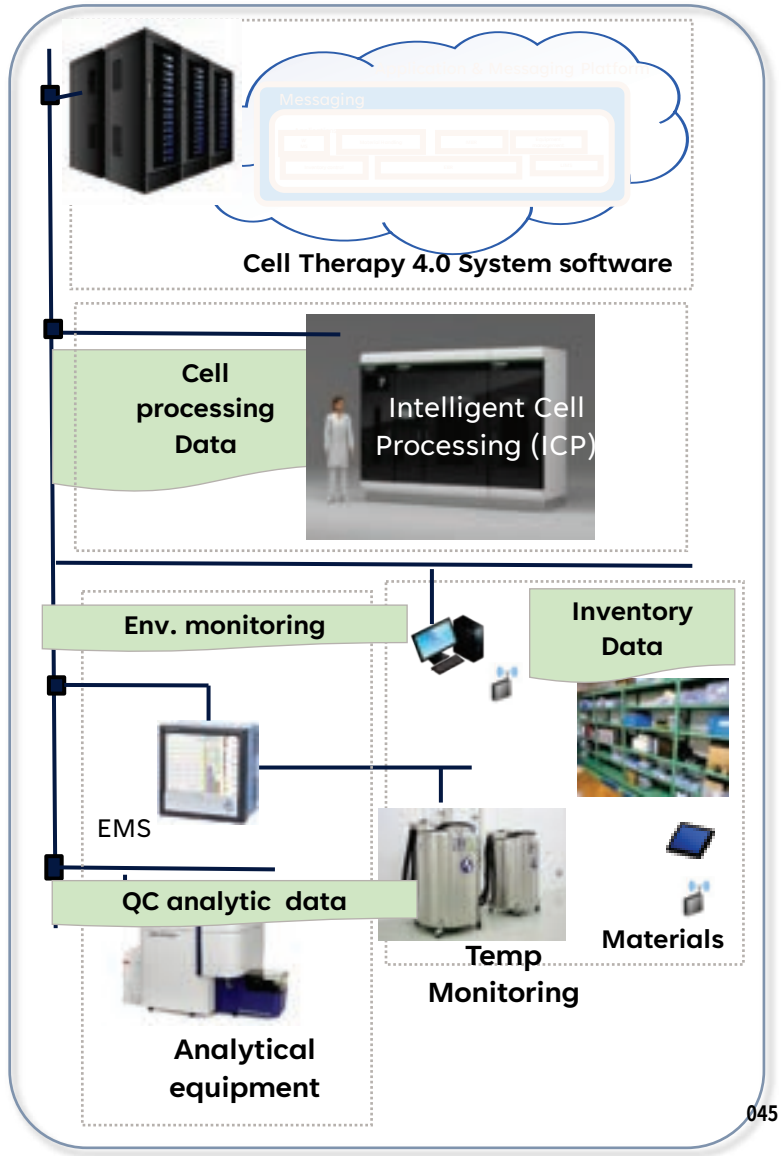
・Central QC Room

QbD based-cell manufacturing Solution Lab in KCMI

SINFONIA



Cloud CF4.0 system



Cyto-Facto is the first CMO/CDMO that can manufacture commercial CAR T for global pharma in Asia

2014 Launched CAR-T CMO project as R&D Center for Cell Therapy (RDC) of the FBRI.
Technology transfer of CAR-T production (Kymriah®) by Novartis.

2017 Cell Processing Center in compliance with PIC/S GMP in the EC building in service.

2018 Began production of the clinical product Kymriah® for the Japanese market.

2020 Obtained approval for manufacture and sale of regenerative medicine products from HA. Commercial production of Kymriah® started.

2021 Technology transfer of MSC production (FF-31501) by Fujifilm.

2022 Completion and operation of the Cell Processing Center (CPC) on the 5th floor of KCMI

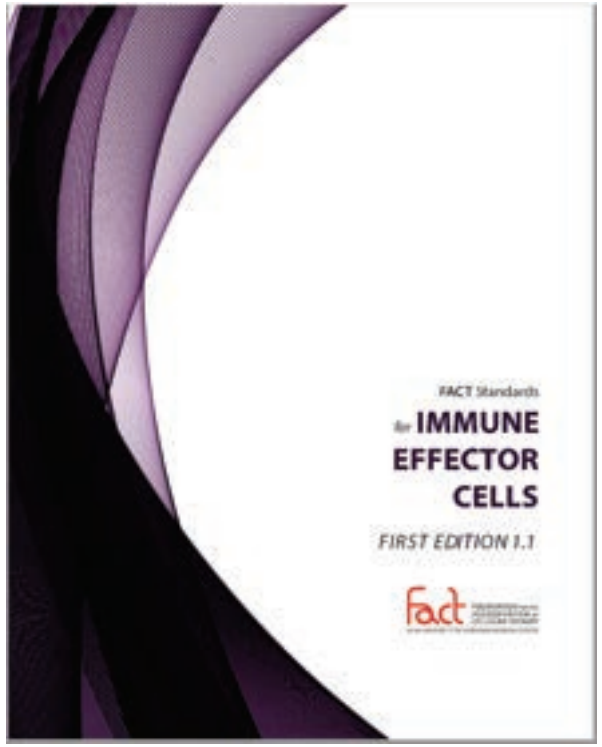
2023 FF-31501 investigational product manufacturing began.
Several process development projects for CAR-T, MSC manufacturing started.

Cyto-Facto supported the dissemination of CAR T
The CAR-T therapy in Japan was started in 2018

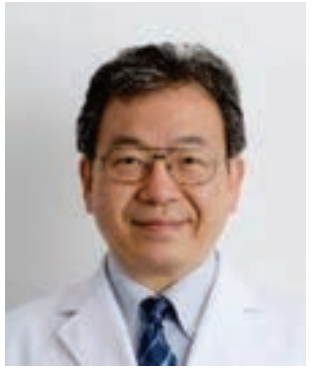
Introduce FACT - Standards for IMMUNE EFFECTOR CELLS to Japanese apheresis sites

Set up and open apheresis sites in Japan for Kymriah manufacturing through the network of Japan Society of Transfusion Medicine and Cell Therapy under the technical support from NPKK.

All of the apheresis sites opened in Japan were set up based on the recommended plans stated in the Q&A in the journal of JSTMCT and web HP.



JSTMCT
The Japan Society of Transfusion Medicine and Cell Therapy



Keio Univ. Hemato
Dr. Tanozaki

Kyoto Univ.Hemato
Dr. Arai

Kyoto Univ. Hemato
FBRI
Kawamata

Network of ARO was utilized to organize the apheresis/hospital sites for CAR-T therapy in Japan

FBRI chairs the Academic Research Organization Liaison Council for Cell Processing Center.

The 17 major academic/governmental medical centers for cell therapy participate Liaison Council.

FBRI promotes the supply of Kymriah and collect the therapy-related issues need to be fixed through this network.

Chaired by FBRI Kawamata

Cyto-Facto has a prestigious Kymriah manufacturing record, with manufacturing success rate of 95% (123 batches/129 batches)

ORIGINAL PAPER

Risk factors for CAR-T cell manufacturing failure among DLBCL patients: A nationwide survey in Japan

Tomoyasu Jo[1,2] | Satoshi Yoshihara[3,4] | Yoshiki Okuyama[5] | Keiko Fujii[6] | Tomoko Henzan[7] | Kaoru Kahata[8] | Rie Yamazaki[9] | Wataru Takeda[10] | Yoshihiro Umezawa[11] | Kentaro Fukushima[12] | Takashi Ashida[13] | Minami Yamada-Fujiwara[14] | Ryo Hanajiri[15] | Noboru Yonetani[16] | Yuma Tada[17] | Yuji Shimura[18] | Hidekazu Nishikii[19] | Norio Shiba[20] | Naoya Mimura[21] | Jun Ando[22] | Takayuki Sato[23] | Yasuhiro Nakashima[24] | Junko Ikemoto[4] | Keita Iwaki[14] | Shin-ichiro Fujiwara[25] | Masaki Ri[26] | Tokiko Nagamura-Inoue[27] | Ryuji Tanosaki[8] | Yasuyuki Arai[1,2]

BJHaem BRITISH JOURNAL OF HAEMATOLOGY

British Journal of Hematology
2023 April 13 Jo et al

Table 1 revised

Factory	2019-2021 Dec	Successful	Failed	successful rate
Novartis Morris Plains NJ US		255	24	91%
Cyto-Facto (FBRI) Kobe Japan		123	6	95%

Cyto-Facto supported reverse translational research

Total 519 cases

manufacturing

DLBCL 438 cases

B-ALL 81 cases

Excluding 30 OOS cases

Success 77 cases
OOS 4 cases
Failure 0 cases

Excl. OOS DLBCL 408 cases

Success
378 cases

Failure
30 cases

compare

JSH（2022/11）/ 64th ASH Oral #664 / Jo T, Arai Y, et al British Journal of Hematology 2023 Scientifc Reports | (2023) 13:14952

Factors determine the success of CAR T manufacturing

PATIENT EPISODES FOR SUCCESS OR FAILURE OF CAR-T THERAPY

Femail 20 s

- Primary mediastinal Large B cell lymphoma
- Treatment
  - DA-EPOCH-R 6 courses ：CR
  - Recurrence→R-ESHAP：no CR
  - R-GCD→Pola BR：no CR
  - **Apheresis →manufacturing OK**
  - IVAC→rediation：PR
  - **CAR-T：CR**
  - No event

Mail 60s

- Diffuse large B lymphoma
- Treatment
  - R-CHOP　1 course：PR
  - BR 4 courses：no CR
  - R-CHASE　1course：PR
  - **Apheresis→manufacturing failure**
  - R-CHASE　2 courses
  - **Apheresis 2→manufacturing failure again**

Additional chemotherapy is not feasible.

Pretreatment conditioning

Factors determine the success of CAR T manufacturing

Bendamustine risk category High risk：> 3 courses, last Tx conducted within 3 M, Middle risk：> 6 courses last Tx conducted 3 after or within 24 M

		Odds ratio	95%CI	p value
Risk by Bendamustine	Low		Reference	
Pretreatment conditioning	Int	**5.520**	(1.436 - 21.215)	0.013*
	High	**57.088**	(3.370 - 966.996)	0.005*
Platelet	Every 10 × 10^4/μL reduction	**2.020**	(1.107 - 3.690)	0.022*
CD4/CD8 ratio	≥1/3		Reference	
	<1/3	**3.249**	(1.314 - 8.036)	0.011*

Interpretation

Case 1

- ✓ Bendamustine ：no use （Low）
- ✓ Platelet：20.0 X 10^4 /μL
- ✓ CD4/CD8 ratio: 1.0 （≥1/3）

Odds ratio

× 57.1
× 2.0
× 3.2
= X **365**

Case 2

- ✓ Bendmustine：6 cycles & rest 2 months （High）
- ✓ Platlet：10.0 X10^4/μL
- ✓ CD4/CD8 ratio: 0.2 （<1/3）

JSH（2022/11）/ 64th ASH Oral #664 Scientific Reports 2023 / Jo T, Arai Y, et al British Journal of Hematology 2023

Innovation that Cyto-Facto takes the lead in C&G therapy as CMO/CDMO

1．Introduction of the QbD-based cell manufacturing system

CellQualia™ ICP System for iPSC and MSC

2．Development of Cloud-type cell manufacturing control system CF 4.0

CF 4.0
CytoFactory 4.0

Automated cell manufacturing system with in-process monitoring that realizes QbD-based manufacturing

Intelligent Cell Processing System CellQualia

Refrigerator module　　Incubation module

SINFONIA　　Cyto-Facto Inc.

- ✓ Closed automated culture system
- ✓ Real-time vision tool
- ✓ In process medium analysis
- ✓ Auto sampling for off-line QC
- ✓ Manufacturing data in IT format

QbD-based Cell manufacturing system has been evaluated by UK Stem Cell under MHRA

Patters Bar
MHRA NIBSC
UK Stem Cell

London

Kobe
KCMI

Comparability test

MHRA trialling pioneering stem cell robot that could transform the availability of life-saving cell therapies - GOV.UK (www.gov.uk)<https://www.gov.uk/government/news/mhra-trialling-pioneering-stem-cell-robot-that-could-transform-the-availability-of-life-saving-cell-therapies>

QbD-based automated cell manufacturing system evaluated by UK Stem Cell, MHRA UK Gov.

https://www.gov.uk/government/news/mhra-trialling-pioneering-stem-cell-robot-that-could-transform-the-availability-of-life-saving-cell-therapies

March 16, 2023

GOV.UK

Home > Health and social care > Medicines, medical devices

Press release

MHRA trialling pioneering stem cell robot that could transform the availability of life-saving cell therapies

The MHRA's UK Stem Cell Bank is one of only two places in the world to test this technology.

From: Medicines and Healthcare products Regulatory Agency, Department of Health and Social Care, and The Rt Hon Steve Barclay MP

Published 16 March 2023

An innovative new robot that grows stem cells, the CellQualia™ Intelligent Cell Processing System, is being trialled by the Medicines and Healthcare products Regulatory Agency (MHRA). This robotic system has the potential to bring safer and more cost-effective treatments to people with a wide range of diseases. It is currently the only one in the world outside of Japan, where it was developed.

This trial is part of a UK-based international research programme, launched in 2021, and a partnership between the MHRA, SAKARTA (a Scottish Regenerative Medicine start-up), and Sinfonia Technology Co. Ltd (a Tokyo-based electrical equipment manufacturer), supported by Foundation for Biomedical Research and Innovation at Kobe (FBRI). The UK Stem Cell Bank is testing the robot over a 12-month period to see whether the cells produced by the fully automated Intelligent Cell Processing System meet the standards needed for them to be used in the manufacture of potentially life-saving treatments.

Example of eBatch Record of MSC

Status

In-line sensor pH, Glu, Lac, CO2

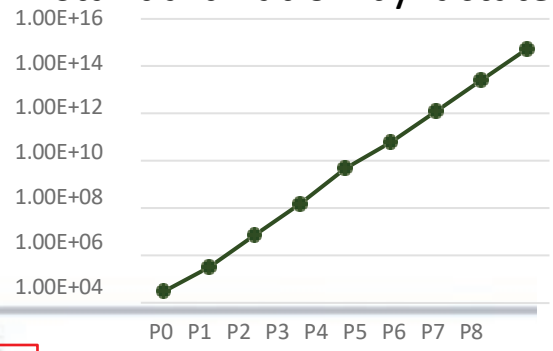
Cell image

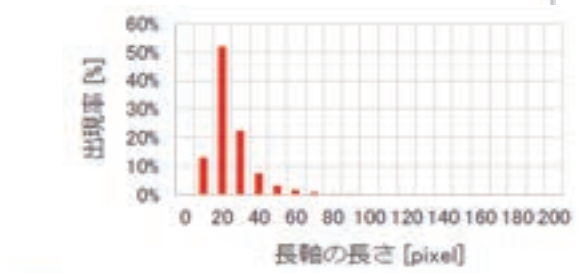
Batch overview

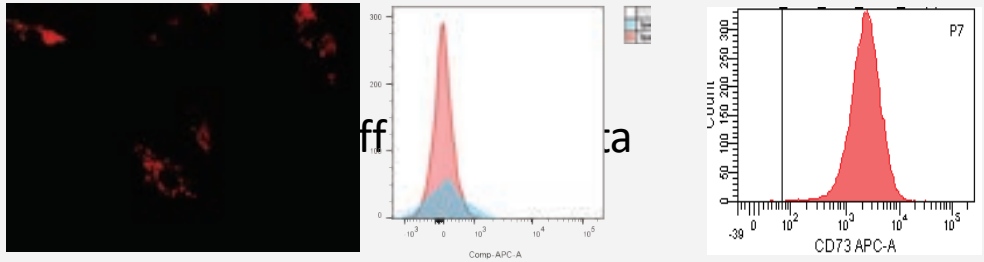
Materials

Event log

Cell count by captured image and standardization by lactate.

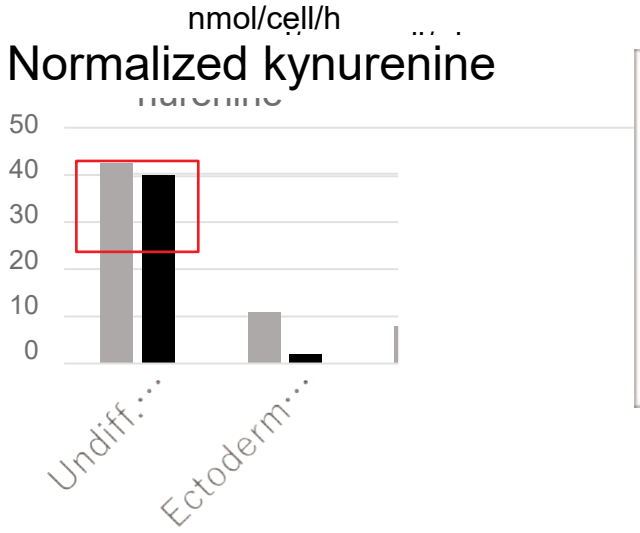




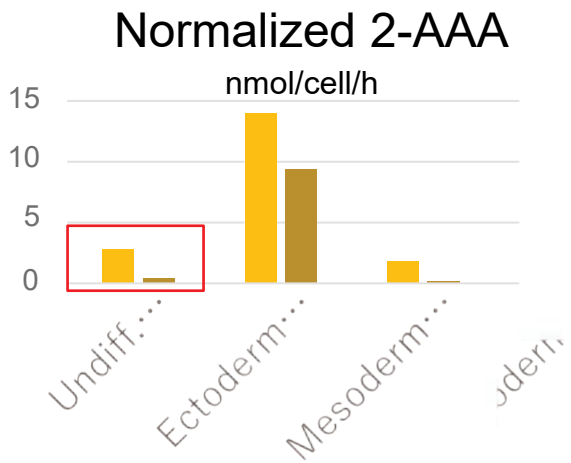


Karyostat HD CNVs ≤3

Example of eBatch Record of iPSC/ESC

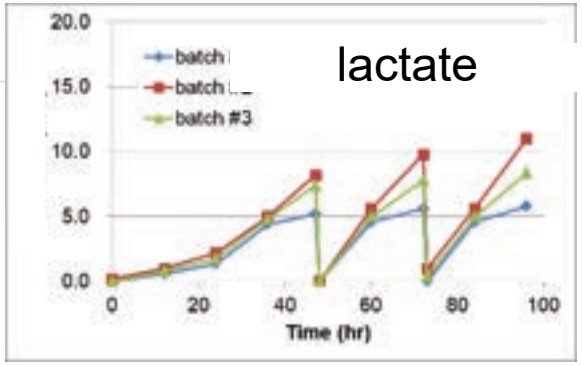


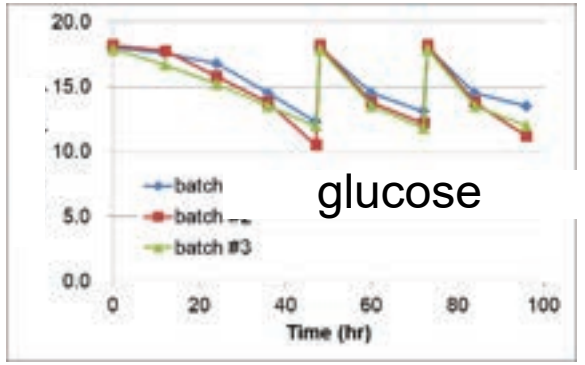
Science signal 2019 Yamamoto et al.

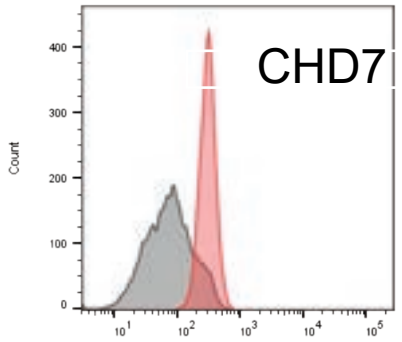


Science signal 2019 Yamamoto et al.

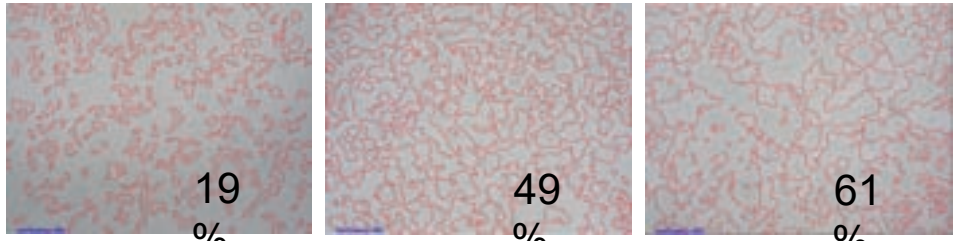
online medium analysis

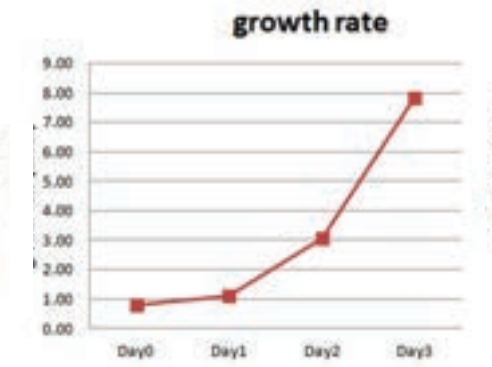


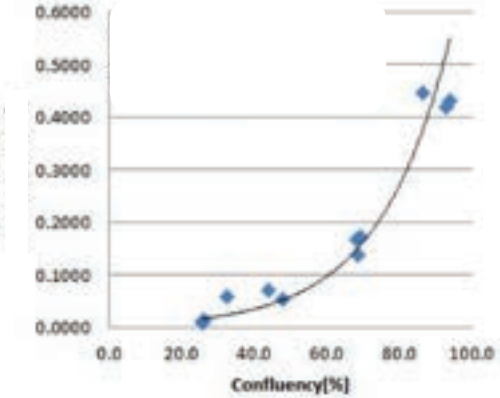


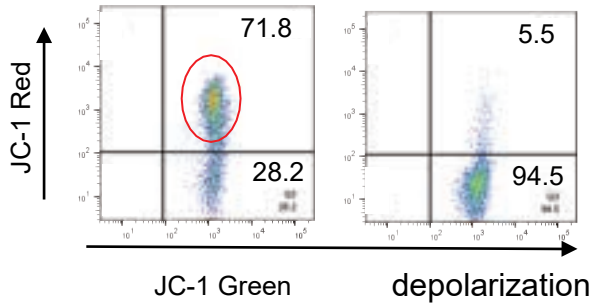


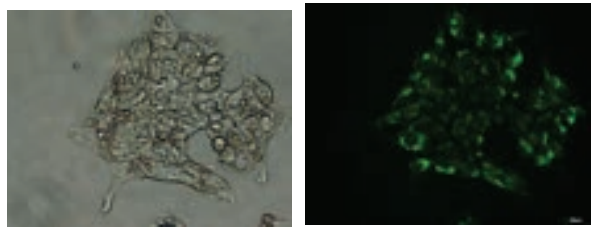
online image analysis



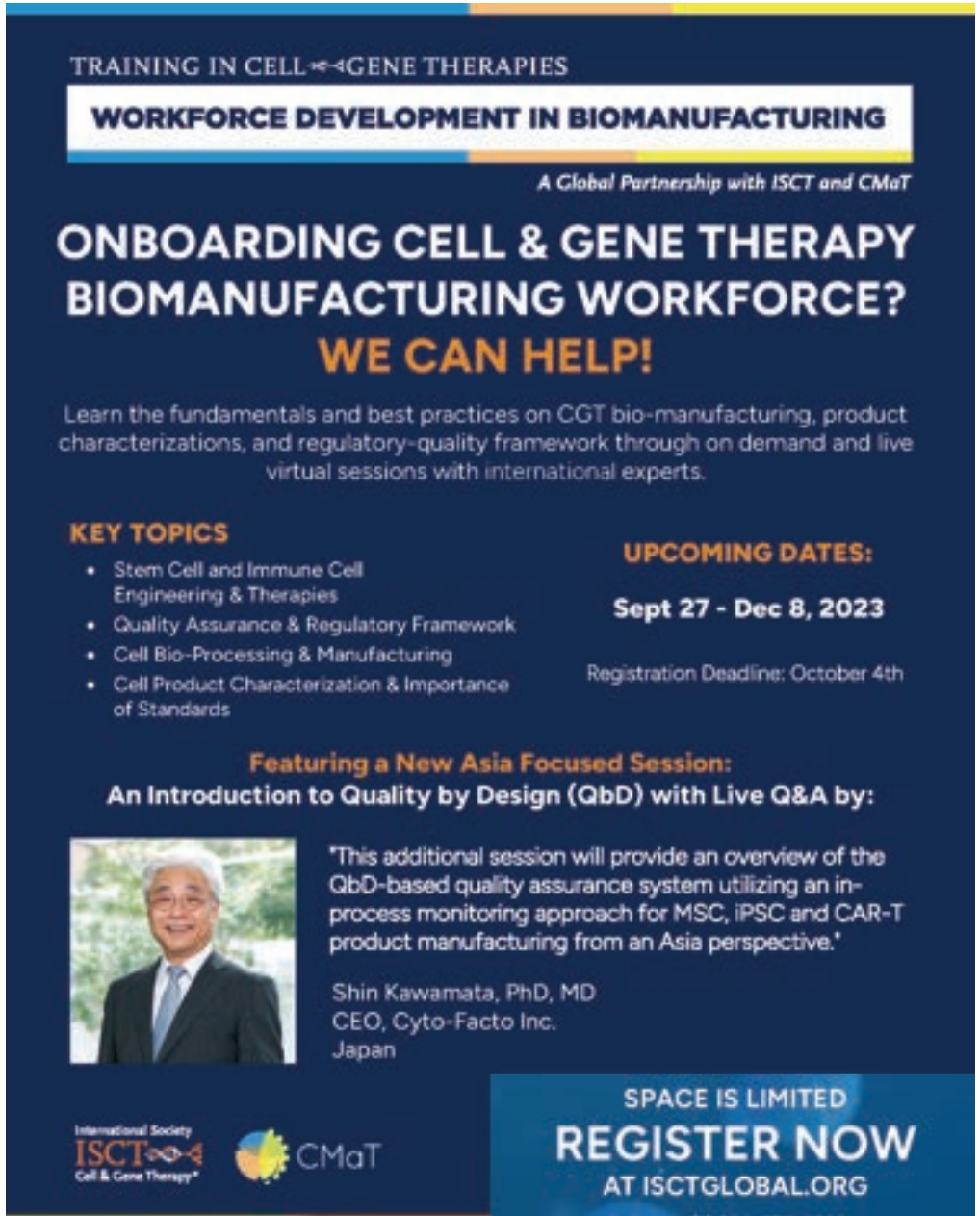








Cyto-Facto promotes QbD-based manufacturing



Introduction to Quality by Design-base Cell manufacturing:
Q&A live on Oct 26 10:00-11:00 (JST)

ISCT Asia Secretory 2020-

ISCT iPSC subcommittee Chair 2021-

ISCT journal CytoTherapy associated editor 2023-

Innovation that Cyto-Facto takes the lead in C&G therapy as CMO/CDMO

1．Introduction of the QbD-based cell manufacturing system

CellQualia™ ICP System for iPSC and MSC

2．Development of Cloud-type cell manufacturing control system CF 4.0

CF 4.0
CytoFactory 4.0

Cloud-based cell manufacturing control software can visualize whole manufacturing process

Cyto-Facto Inc.

Material receiving
Inventory creation (RFID)

Return inventory
Clean out stock

Batch Mgmt.
(QA Status)

Move to Packing area
One Step Transportation

Move to Kitting room
One Step Transportation

Manufacturing Order
Shop Floor Order

MBR execution
Kitting (RFID)

MBR execution
Media Preparation

Return to warehouse
One Step Transportation

Disposal
Clean out stock

Can be used for any cell manufacturing and analytical method via cloud.

MBR execution
MO & SFO for
Cell Processing

Historic

Inline data, log
Time, Weight, …

Electronic Batch Record

LIMS

QC devices

Off line Sampling

Shipping decision
One Step Transportation
Batch mgmt.

storage

Shipping
Clean out stock

Temperature

Pressure diff.

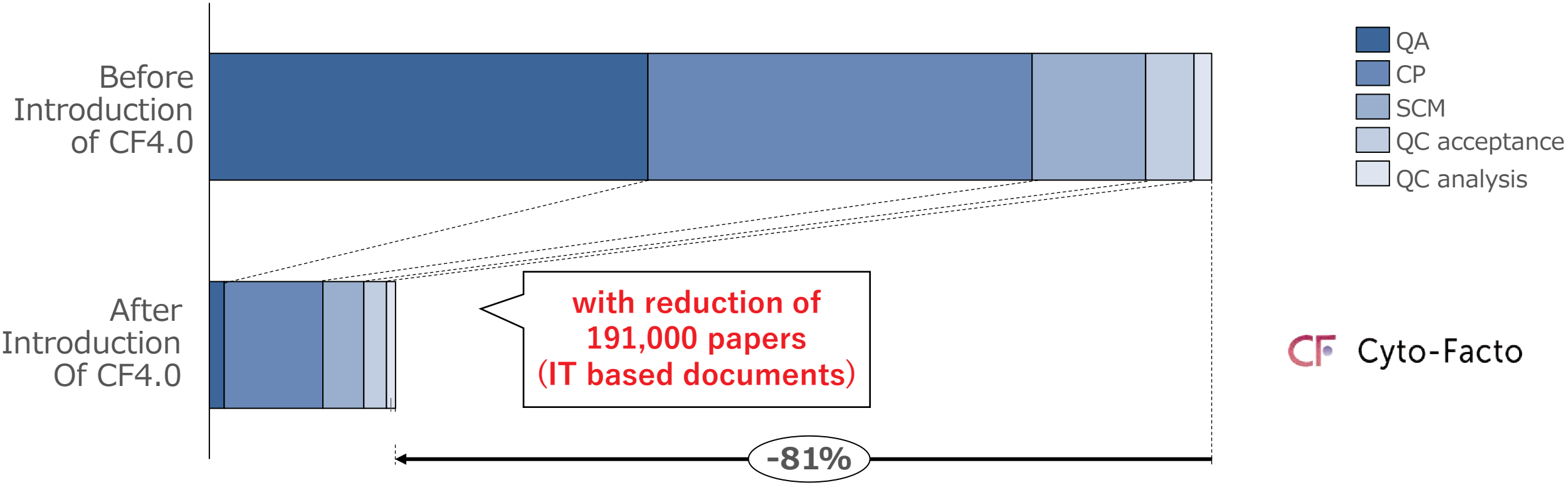
…

EMS

Particle

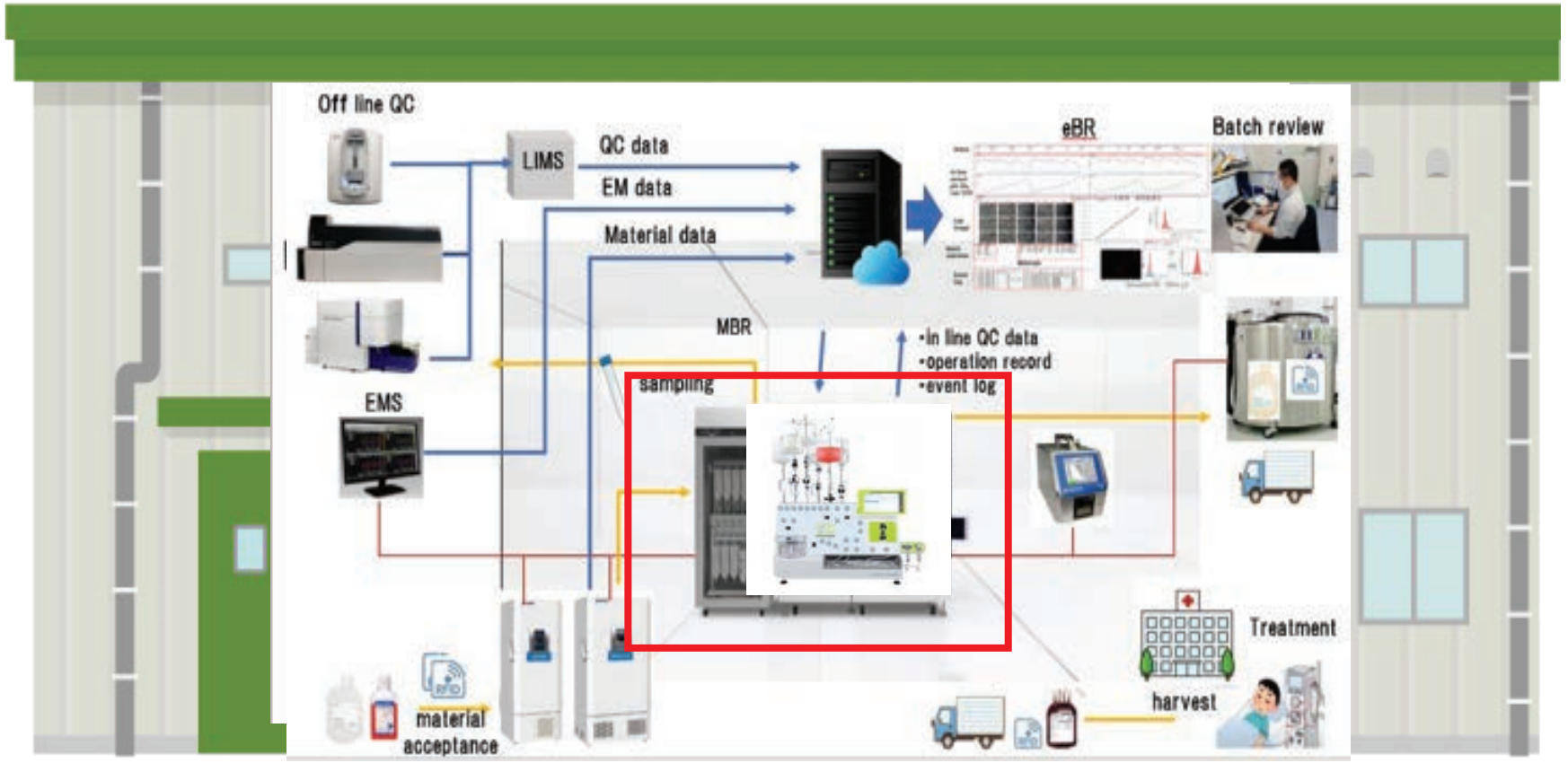
Reduction of working hours through introduction of CF 4.0 software

Premise　8 batches/month unit ：hour

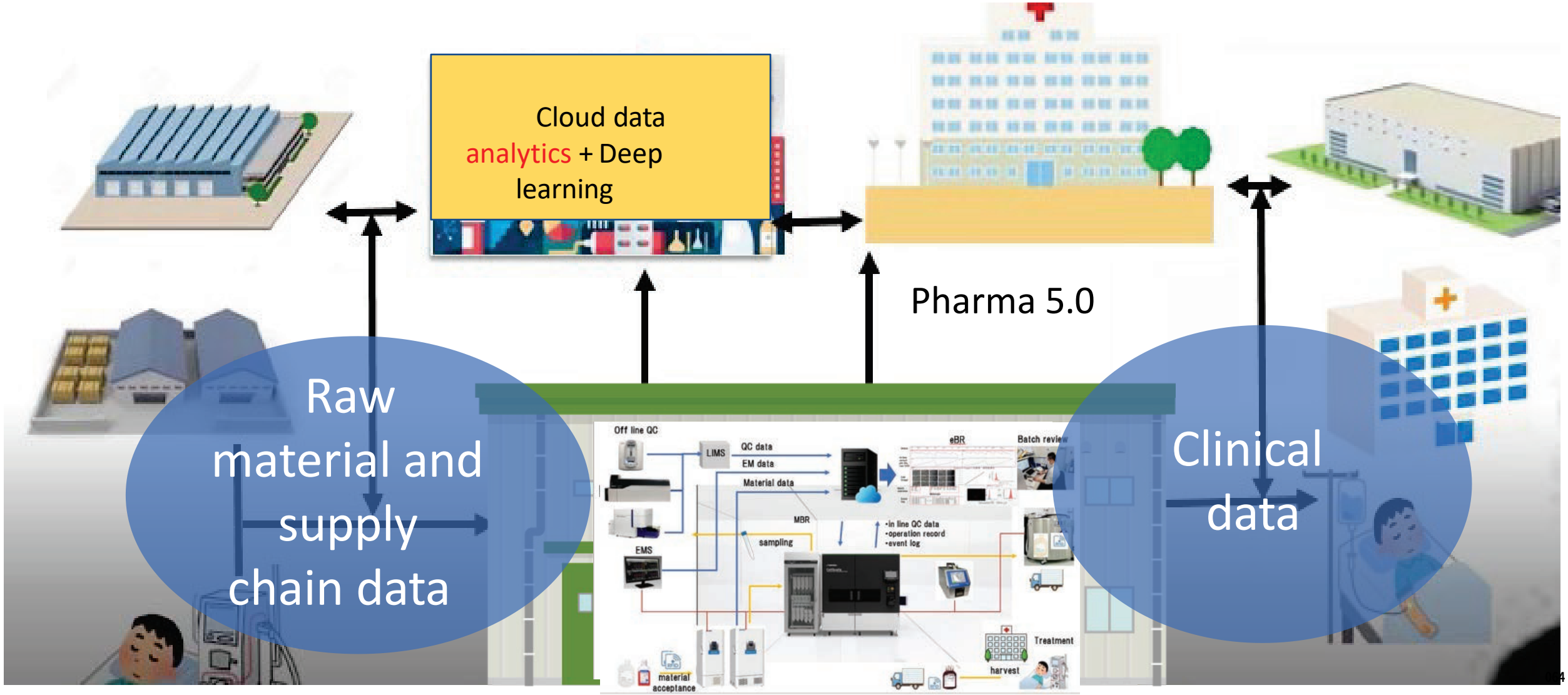


Cyto-Facto

Manufacturing information in IT format can enable linkage to production data, inventory, shipping and ERP in site



Manufacturing information in IT format can enable linkage to manufacturing, supply chain and clinical data

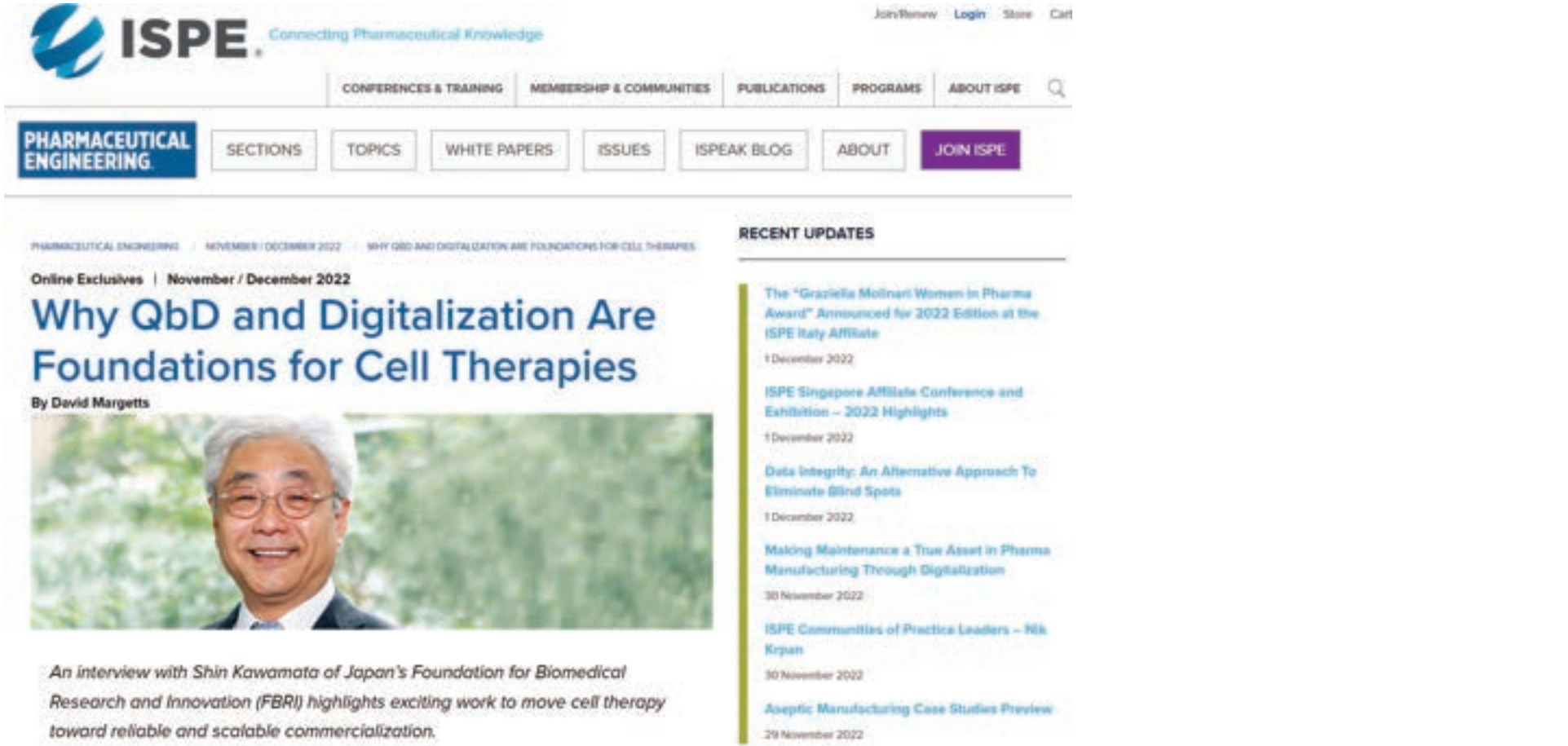


Cyto-Facto promotes the IT-based cell manufacturing control

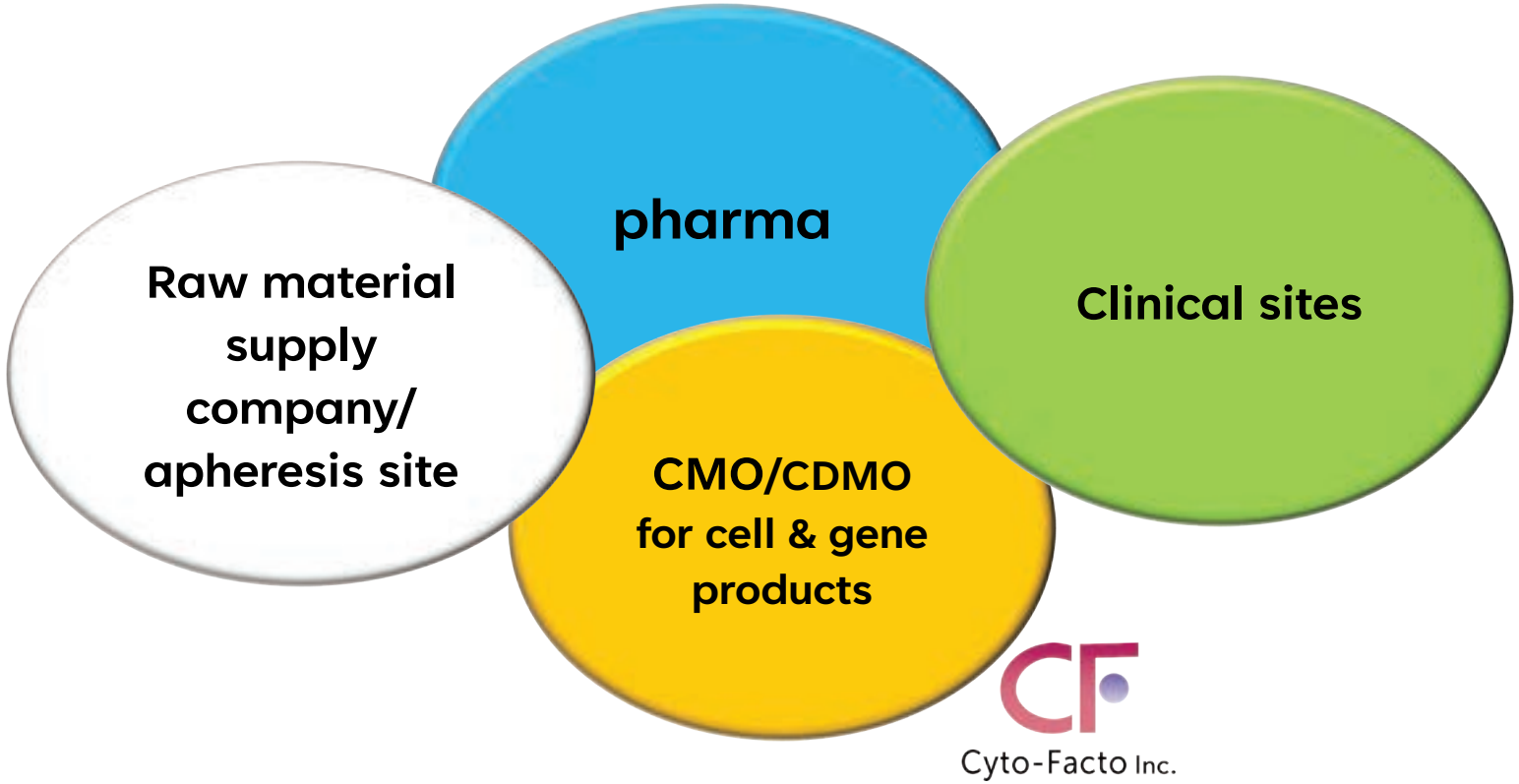
“Digitization is essential for cell manufacturing”

Online Exclusives | November/December 2022

https://ispe.org/pharmaceutical-engineering/november-december-2022/why-qbd-and-digitalization-are-foundations-cell

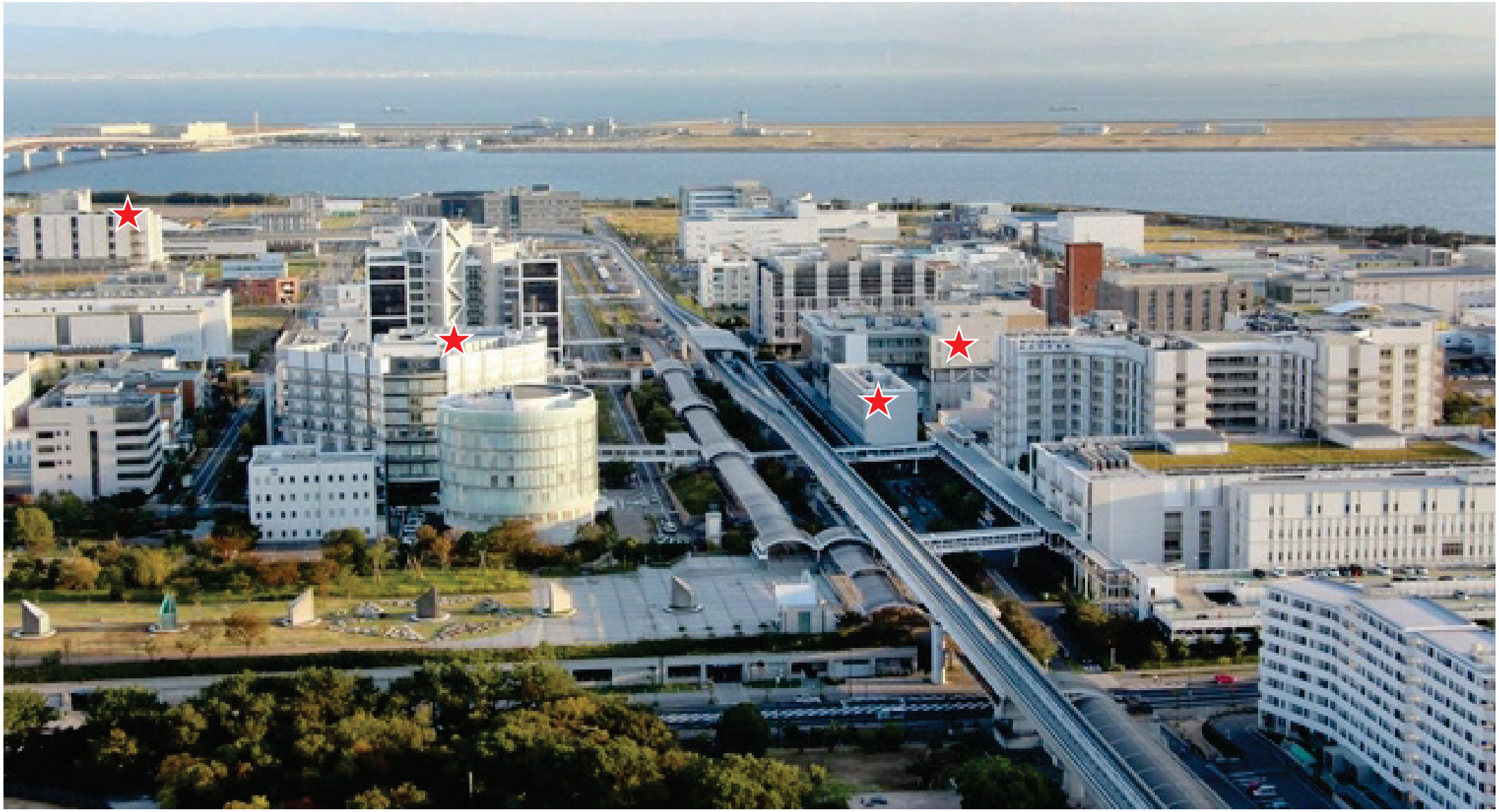


Cyto-Facto supports the development of C&G products with IT-based manufacturing data.



Cyto-Facto is seeking business partners to promote new CMO/CDMO business model in C&G therapy

★Cyto-Facto facilities and offices located in Kobe BioMedical Cluster



Thank you for your attention

株式会社ジャパン・ティッシュエンジニアリング
Japan Tissue Engineering Co., Ltd.
https://www.jpte.co.jp

J-TEC

https://www.jpte.co.jp

再生医療をあたりまえの医療に

Creating a Future for Regenerative Medicine

1999年に再生医療の産業化を目指して活動を開始してから、
私たちは、患者さまの細胞から製品をつくり、提供する経験を積み重ねてきました。
これから、もっとたくさんの患者さまに私たちの経験を提供したい。
表皮、軟骨、角膜領域だけでなく、
あらゆるケガや病気を再生医療製品で治せるようにしたい。
いつか、「再生医療」が「あたりまえの医療」になり、
誰もが、いつでも、どこでも、身近に再生医療を受け、健康を維持することができる、
そんな世の中の実現を目指し、さまざまな領域への挑戦を続けます。

Since starting work to commercialize regenerative medicine in 1999,
we have accumulated experience in creating and supplying products made from patients' cells.
In the future, we want to offer our experience to even more patients.
We want to use regenerative medical products to cure all kinds of injuries and diseases,
not just in the fields of epidermis, cartilage and cornea.
Someday, regenerative medicine will be a standard healthcare.
We continue to strive in all kinds of fields to create a reality
in which everyone can enjoy the benefits of regenerative medicine
close at hand anytime and anywhere to maintain their health.

企業理念 Corporate Philosophy

再生医療の産業化を通じ、社会から求められる企業となる。
法令・倫理遵守の下、患者様のQOL向上に貢献することにより、人類が生存する限り成長し続ける企業となる。
その結果、全てのステークホルダーがより善く生きることを信条とする。

Through the industrialization of regenerative medicine,
being a company essential and valuable to society.
By contributing to patient QOL on the basis of legal and ethical compliance,
being a company that continues to grow and evolve as long as the human race exists.
We hold the philosophy that all stakeholders will achieve a better life as a result.

INDEX

再生医療とは

What is Regenerative Medicine?

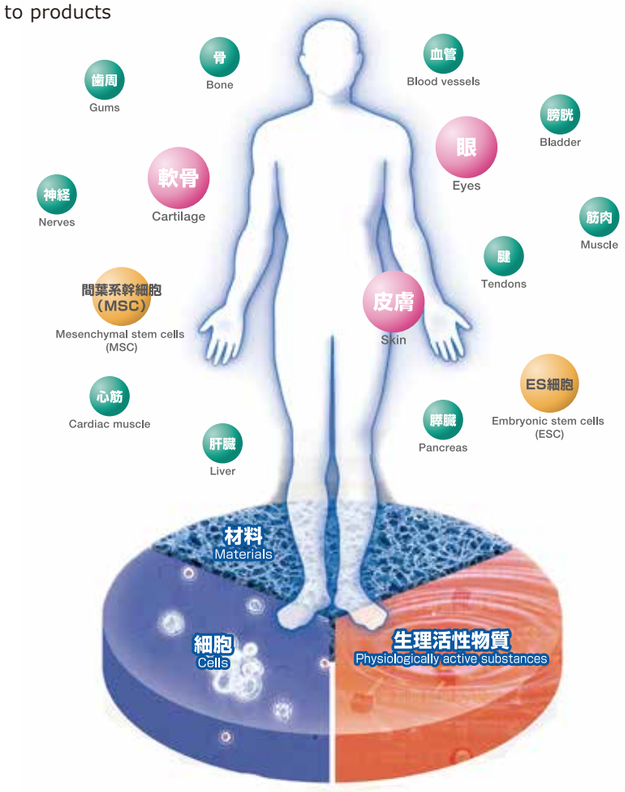
再生医療の実現に向けて

失われた組織・臓器を再生できたら、素晴らしいことです。現在、この再生を目的とした新しい医療「再生医療」が始まっています。その中には、例えば私たち自身の細胞を使う方法があります。本人の細胞を体外でたくさん増やして治療に使えば、少しの組織を取るだけで済むため、取られた部分にはほとんど障害が残りません。また、自分自身の細胞なので免疫拒絶反応を引き起こすこともないのです。もちろん、ドナーとなる方を待つ必要もありません。高度に発展したティッシュエンジニアリングの手法を使って、私たち自身の細胞から私たち自身の体の一部をつくり出すのです。
1993年、米国のJ.VacantiとR.Langerは「細胞、材料、生理活性物質」を適切に組み合わせて人工組織・臓器をつくり出すという新しい概念を提唱しました。培養した細胞を移植するには、それに相応しい、体になじみやすい材料が必要になります。さらに、細胞がより元気な状態で移植されるために種々の生理活性物質も使われます。ティッシュエンジニアリングは、再生医療の実現に向けた新しい手法であり、J-TECの社名には日本でティッシュエンジニアリングを確立する決意が込められています。

Making Regenerative Medicine a Reality

How wonderful it would be to be able to regenerate lost tissues or organs. A new branch of medicine that aims to achieve just that is now beginning to take shape: regenerative medicine. One method used in this new field, for example, utilizes our own cells. Growing a large volume of the patient's own cells outside the body for use in treatment would require only a small amount of tissue, meaning there would be minimal damage to the area of the body from which it was taken. As the cells would be the patient's own, they would not cause an immune rejection. Of course there would be no need to wait for a suitable donor to come forward. Regenerative medicine uses highly developed techniques of tissue engineering to create a part of our own body from our own cells.
In 1993, Joseph Vacanti and Rovert Langer proposed the then-novel concept of the creation of artificial organs or tissues through the appropriate combination of cells, materials, and physiologically active substances. The transplantation of cultured cells requires an appropriate material that is easily accepted by the body. In addition, a number of different physiologically active substances are necessary in order to transplant cells in a healthier state. Tissue engineering is a new means toward making regenerative medicine a reality. J-TEC's name signifies our determination to establish tissue engineering in Japan.

ティッシュエンジニアリングの
三要素と応用製品例
The three elements of tissue engineering and their application to products



自家培養表皮
Autologous Cultured Epidermis

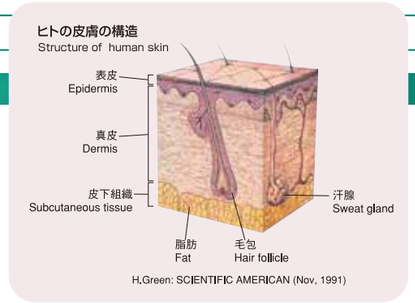
世界で最も広く使われている再生医療製品が培養表皮。
J-TECの培養表皮は、日本の再生医療等製品第1号です。

Cultured epidermis is the world's most widely used human cellular and tissue-based product.
J-TEC's cultured epidermis is the first approved regenerative medical product in Japan.

培養表皮とは　What is cultured epidermis?

ヒトの皮膚は、宇宙における宇宙服と同様、地球上においても生体内と外界とを遮断する目的で体表面を隙間なく覆っています。総面積は成人で平均1.6m²、総重量は皮下組織を含めると約9kgに達し、"最大の臓器"ともいわれます。例えば熱傷（やけど）などで皮膚が広範囲に失われると、体温の維持や水分の保持といった生命機能に重大な支障をきたし、さらには外界から侵入する菌による感染症が原因で命を落とす危険性が高くなります。ただし小さな切り傷や擦り傷が数日で治癒することからも分かるとおり、皮膚は高い再生能力を有しています。
組織学的にみると皮膚は上から表皮、真皮、皮下組織の順に層を形成していますが、表皮を構成する表皮細胞の増殖能力が非常に優れているため皮膚は速やかに再生します。しかし、広範囲に皮膚が失われた場合には再生が間に合いません。そこで正常な皮膚から表皮細胞を取り出してフラスコで培養し、皮膚のようにシート状にして受傷部位に移植する培養表皮が開発されました。

The entire human body is covered by skin. An average adult has a total surface area of around 1.6 m² of skin, which, if subcutaneous tissue is included, weighs around 9 kg. Skin is the largest organ of the human body. If a burn or other trauma results in skin loss over a wide area, this seriously impairs the skin's vital functions of maintaining body temperature and conserving fluids, and infection by bacteria that invade the body from outside also increases the risk of death. Histologically, skin comprises three layers: from the outside in, these are the epidermis, dermis, and subcutaneous tissue. The keratinocytes that compose the epidermis possess an extremely high ability to proliferate, meaning that skin regenerates very rapidly. When skin is lost over a wide area, however, regeneration takes too long. Prominent scientists have developed a cultured epidermis that can be grafted in such injured area. This epidermis is made by isolating keratinocytes from a skin biopsy, culturing them in flasks, and growing them into a skin-like sheet.



開発者　Researchers

J-TECは、世界有数の研究者から再生医療の産業化を託され、技術協力を得ながら共同研究を続けています。

The world's leading reseachers have entrusted the industrialization of regenerative medicine to J-TEC. With their technical cooperation, we are continuing to carry out collaborative research.

Howard Green, M.D.

再生医療における表皮幹細胞生物学の世界的権威で、Green型培養表皮の開発者。1970年代にマウスの線維芽細胞と共に培養して表皮細胞シートを作製する手法を開発した。
ハーバード大学医学部名誉教授、アメリカ（2015年没）

A world authority in the field of epithelial stem cell biology, and the father of a method now known as Green's technique for culturing epidermis. The late Prof. Green developed a technique in the 1970s that involved culturing keratinocytes together with mouse fibroblasts to form a keratinocyte sheet. He was Emeritus George Higginson Professor of Cell Biology, Harvard Medical School, U.S.A. (d. 2015)

熊谷憲夫 先生
Norio Kumagai, M.D., Ph.D.

培養表皮を用いた臨床治療の世界的権威。専門は形成外科、再生医療。
聖マリアンナ医科大学 名誉教授、日本

A world authority on the use of cultured epidermis in clinical treatment. He is a professor emeritus at St. Marianna University, School of Medicine, JAPAN

Michele De Luca, M.D.

再生医療における表皮幹細胞生物学の世界的権威。重症熱傷の治療のために欧州で初めて培養表皮幹細胞の移植を行った。
Modena and Reggio Emilia大学教授、イタリア

A world authority in the field of stratified epithelial stem cell biology, Prof. De Luca was the first person in Europe to carry out the transplantation of cultured epithelial stem cells. He is Professor of Biochemistry, Director of Center for Regenerative Medicine in the Department of Life Sciences, University of Modena and Reggio Emilia, Italy.

開発の経緯　Development

表皮細胞は増殖能力に優れているものの、フラスコでの培養は困難でした。1970年代に米国ハーバード大学医学部Howard　Green教授がマウスの線維芽細胞*と共に培養して表皮細胞シートを作製する手法を開発しました。その手法を用いたのがGreen型培養表皮です。そして1984年、重症熱傷の幼児2人にわずかに残った皮膚から5千～7千cm²のGreen型培養表皮を作製・移植して救命に成功し、世界的に注目されました。海外では多くの細胞を使った製品がありますが、Green型培養表皮は各国の細胞培養製品の開発において常にトップランナーです。J-TECは日本初のヒト細胞を用いた再生医療等製品としてGreen型培養表皮を開発しました。

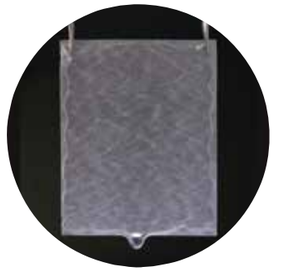
In the 1970s, Professor Howard Green of Harvard Medical School developed a method that involved culturing keratinocytes together with mouse fibroblasts* to form a keratinocyte sheet, a method now known as the Green's technique for culturing epidermis. In 1984, it attracted worldwide attention when the lives of two severely burned children were saved by this technique, which was used to generate 5,000-7,000 cm² of cultured epithelium for grafting from what little healthy skin remained to the patients. Many human cellular and tissue-based products are available worldwide, and cultured epidermis prepared by Green's technique has invariably played a major role in advancing the development of regenerative medicine in different countries. J-TEC has developed a cultured epidermis using Green's technique as Japan's first regenerative medical product utilizing human cells.

*マウスの線維芽細胞：H.Green教授が樹立した表皮細胞の培養に最適な3T3-J2細胞株。過去30年以上の臨床使用で安全性が確立されている。
*Mouse fibroblasts: The 3T3-J2 cell line is the most suitable for keratinocyte cultivation according to the technique established by Professor H. Green. Their clinical safety has been confirmed in over 30 years of clinical use.

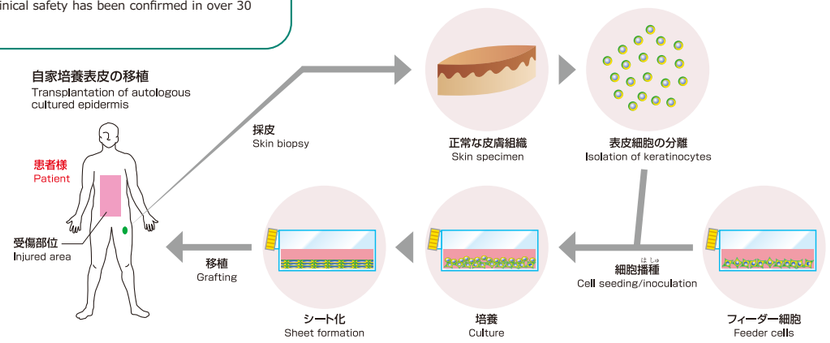
培養方法　Culture

J-TECでは名古屋大学の上田実教授から技術移転を受け、開発者であるH.Green教授と世界的な臨床的権威であるMichele De Luca博士の指導の下で多くのノウハウを蓄積しており、世界最高水準のGreen型培養表皮を作製する技術を有しています。下図に示した通り1cm²程度の正常な皮膚組織から表皮細胞を分離して培養すると、約2週間で1千cm²を超える培養表皮シートを作製することができます。

The technology for keratinocyte cultivation has been transferred to J-TEC by Professor Minoru Ueda of Nagoya University. J-TEC has accumulated expertise under the guidance of Professor H. Green, who developed the technique, and clinical authority Dr. Michele De Luca, and now possesses the skills to generate cultured epidermis that meets the highest global standards, using Green's technique. By isolating keratinocytes from a 1-cm² skin sample and culturing them as illustrated below, a sheet of cultured epidermis measuring around 1,000 cm² can be produced in around two weeks.



培養表皮
Cultured epidermis



製品化　Commercialization

自家培養表皮（販売名：ジェイス）は、2007年10月に重傷熱傷の治療を目的として厚生労働省より製造販売承認を取得、2009年１月より保険適用を受けました。我が国第1号の再生医療等製品です。
また、2016年９月には先天性巨大色素性母斑の治療、2018年12月には表皮水疱症（栄養障害型及び接合部型）の治療を目的として一部変更承認を受けました。これは、再生医療等製品では国内初の適応拡大*です。

*医薬品医療機器等法による製造販売承認では、適応対象が明確に決められていますが、治療対象となる疾患の種類を増やすことを「適応拡大」といいます。

Autologous Cultured Epidermis (product name: JACE) received approval in October 2007 from the Ministry of Health, Labor and Welfare for the indication of severe burns, and has been listed as an item covered by the national health insurance since January 2009. JACE is the 1st regenerative medical product in Japan.
Also, JACE received approval for additional indications for giant congenital melanocytic nevi in September 2016, and for dystrophic and junctional epidermolysis bullosa in December 2018. This approval marks the first time the indication of a regenerative medical product is extended in Japan*.

*Under the Pharmaceutical and Medical Device Act, the indication for a regenerative medical product is clearly specified. Extending the indication to different conditions requires government approval.

自家培養軟骨
Autologous Cultured Cartilage

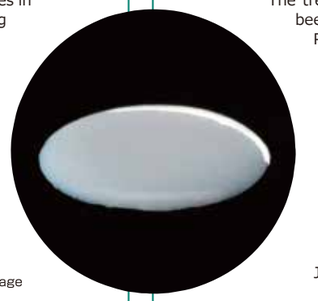
J-TECの培養軟骨は、日本の再生医療等製品第2号です。
自らの軟骨により、本来の滑らかな関節の動きを。

J-TEC's cultured cartilage is the second approved regenerative medical product in Japan.
Move your joints just as smoothly as you used to.

培養軟骨とは　What is cultured cartilage?

軟骨は膝や肘などの関節の骨の表面を薄く覆っていて、関節の動きを滑らかにする役割を果たしています。健常な成人で厚みは約2～3mmといわれ、加齢と共に薄くなります。軟骨組織はケガなどで一度損傷を受けると自然には治らないため、薬などで治療することは非常に困難です。体内では自然治癒できない軟骨を、最新のティッシュエンジニアリング技術を用いてシャーレの中で作製したものが培養軟骨です。

Cartilage is the thin layer that covers the bones in joints such as knees and elbows, allowing them to move smoothly over each other. In healthy adults this layer is around 2-3 mm thick, but it becomes thinner with advancing age. As cartilage tissue does not naturally recover once damaged, it is extremely difficult to treat it with drugs or other therapies. Now, however, with the latest tissue-engineering technology, cartilage can be regenerated in a culture dish as cultured cartilage.



培養軟骨
Cultured cartilage

開発の経緯　Development

軟骨の損傷を治療することは整形外科学の長年の目標でした。広島大学の越智光夫教授は、軟骨の損傷を受けた患者様から軟骨を少量採取して培養軟骨をつくり、再び手術で欠損部へ戻す治療法（自家培養軟骨移植術）を確立しました。J-TECはこの方法に早くから注目し、越智教授から培養方法の指導を受けて、これまでに様々な試験を実施し、日本初となる培養軟骨の再生医療等製品を開発しました。

The treatment of damaged cartilage has long been one of the aims of orthopedic surgery. Professor Mitsuo Ochi of Hiroshima University has taken small amounts of cartilage from patients with cartilage damage and produced cultured cartilage, which is then used in surgery to repair the defective area. The therapeutic technique he established is known as autologous cultured cartilage transplantation. J-TEC was quick to take notice of this method and obtained the guidance of Professor Ochi in order to develop Japan's first ever cultured cartilage.

開発者　Researchers

越智光夫 先生
Mitsuo Ochi, M.D., Ph.D.

軟骨欠損治療のための再生医療を行う世界的権威。専門は膝関節外科、スポーツ医学、再生医学。組織工学的手法を用いた関節軟骨欠損に対する治療を1996年より日本で開始。J-TEC自家培養軟骨の開発を支援。
広島大学学長　整形外科医、日本

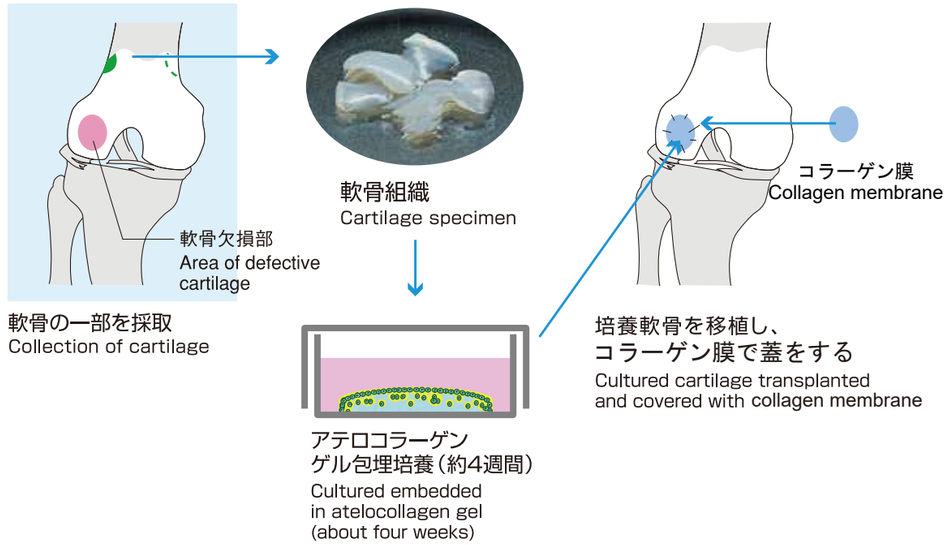
A world authority on the use of regenerative medicine in the treatment of cartilage defects. Professor Ochi is a specialist in knee-joint surgery, sports medicine, and regenerative medicine. He started therapy for knee-joint cartilage defects using tissue-engineering techniques in Japan in 1996. He has advised J-TEC on the development of autologous cultured cartilage. He is Orthopaedic Surgeon, and President of the Hiroshima University, Japan.

培養方法　Culture

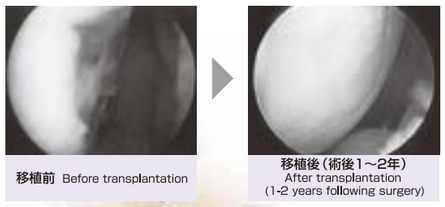
整形外科の専門医によって、侵襲の少ない関節鏡手術で膝の軟骨が少量採取されます。この軟骨をJ-TECに運んで細胞を分離し、ゲル状のアテロコラーゲンと混合して立体的な形に成形した後、培養します。約4週間の培養期間中に軟骨細胞は増殖し、基質を産生して本来の軟骨の性質に近くなっていきます。この方法は三次元培養方法と呼ばれ、軟骨細胞が本来持っている性質を維持したまま培養できる、とても優れた方法です。

An orthopedic surgeon carries out minimally invasive arthroscopic surgery (keyhole surgery) to collect a small amount of cartilage from the knee. This cartilage is sent to J-TEC and cultured after having been mixed with atelocollagen gel and shaped into a three-dimensional form. During the culture period, which lasts about four weeks, the cartilage cells (chondrocytes) proliferate and eventually reach a state closely resembling the properties of the original cartilage. This method is known as three-dimensional culture, and it is outstanding for the fact that it enables chondrocytes to be cultured while retaining their original properties.

自家培養軟骨の移植（膝関節）
Transplantation of autologous cultured cartilage (knee-joint)



関節鏡による移植前と移植後の様子
Arthroscopic images before and after transplantation



移植前 Before transplantation
移植後（術後1～2年）
After transplantation
(1-2 years following surgery)

関節の欠損部に自家培養軟骨を移植すると、もとの形に再生する
Transplantation of autologous cultured cartilage into the defective area of the joint results in the restoration of its original shape

Ochi M. et al., J. Bone Joint Surg. (2002)

製品化　Commercialization

自家培養軟骨（販売名：ジャック）は、2012年７月に厚生労働省より製造販売承認を取得し、2013年４月より保険適用を受けています。整形外科領域における我が国初の再生医療等製品です。
適応対象は、膝関節における外傷性軟骨欠損症又は離断性骨軟骨炎（変形性膝関節症を除く）であり、他に治療法がなく、かつ軟骨欠損面積が４cm^2以上の軟骨欠損部位に適用する場合に限るとされています。

Autologous Cultured Cartilage (product name: JACC) received approval from the Ministry of Health, Labor and Welfare in July 2012, and has been listed as an item covered by the national health insurance since April 2013. JACC is the first regenerative medical product in Japan's orthopedic field.
Its indication is strictly limited to traumatic cartilage defects and osteochondritis dissecans (OCD), excluding osteoarthritis (OA) for knee joints. In addition, the defect area must be over 4 cm^2.

培養角膜上皮・培養口腔粘膜上皮

Cultured Corneal Epithelium・Cultured Oral Mucosal Epithelium

これまで治療法のなかった眼の疾患に
再生医療により新しい希望の光を。

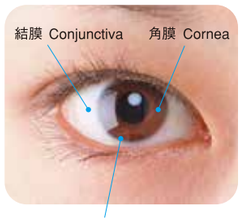
Regenerative medicine offers a new hope
for formerly untreatable eye disorders.

培養角膜上皮・培養口腔粘膜上皮とは　What is cultured corneal epithelium・cultured oral mucosal epithelium?

角膜上皮は眼の角膜最表層に存在し、角膜上皮を経常的に維持するために必要な幹細胞は角膜と結膜の境にある輪部といわれる部分に存在します。角膜に重度の傷害を受けた場合、わずかでも正常な輪部が残っていれば、その輪部組織から角膜上皮細胞を分離して培養することにより自家培養角膜上皮をつくることができます。また、正常な輪部が残っていなければ、口腔粘膜から口腔粘膜上皮シートをつくることができます。これらを移植することにより、従来治療法のなかった角膜疾患を治療することが可能です。

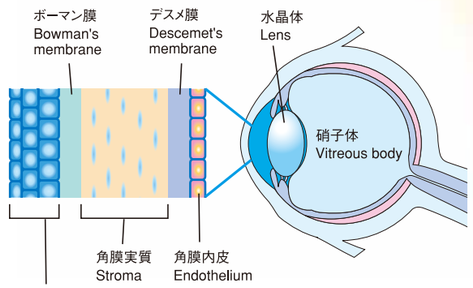
The corneal epithelium forms the outermost layer of the cornea in the eye. Within the corneal epithelium, stem cells are found in the region called the limbus on the border between the cornea and the conjunctiva. In cases of severe injury to the cornea, as long as even a small patch of healthy limbus remains, corneal epithelial stem cells can be isolated from this limbal tissue and cultured to produce autologous cultured corneal epithelium. If there is no healthy limbus remaining, an oral mucosal epithelial sheet can be made from the oral mucosa. Transplanting these tissues makes it possible to treat corneal diseases for which there was no conventional treatment.

眼の各部名称
Structure of human eye



輪部：角膜と結膜の境界にあり、角膜上皮細胞の幹細胞が存在する。
Limbus: Located at the border between the cornea and conjunctiva, this is where corneal epithelial stem cells are found.

角膜の構造
Structure of cornea



角膜上皮：角膜最表層に存在する部分で角膜上皮細胞からなる。
Epithelium: The outermost layer of the cornea, composed of corneal epithelial cells.

培養角膜上皮
Cultured corneal epithelium

培養口腔粘膜上皮
Cultured oral mucosal epithelium

開発の経緯　Development

輪部がセメントや石灰、ペンキ、強力な洗剤などによって傷害を受けると角膜に結膜が侵入し、角膜の瘢痕化（結膜化）が起こります。この角膜に、亡くなった方から提供された角膜（アイバンクの角膜）を移植しても、輪部の角膜上皮幹細胞が存在しないため効果がなく、従来は治療法がありませんでした。このような患者様に培養角膜上皮を移植すると、結膜の侵入が抑えられ治癒することが1997年にイタリアのGraziella Pellegrini博士とMichele De Luca博士らによって世界で初めて示されました。J-TECは株式会社ニデックからの委託を受け、Pellegrini博士らの技術を導入して培養角膜上皮を開発しました。また、培養口腔粘膜上皮は大阪大学大学院医学系研究科（脳神経感覚器外科学（眼科学））の西田幸二教授が開発した技術を導入して開発しました。

When the limbus is damaged, the conjunctiva invades the cornea resulting in scarring (conjunctivalization) of the tissue. Even transplantation of a cornea from a deceased donor has not proved to be a successful means of treatment, as the absence of limbal stem cells results in the worsening of symptoms. In 1997, Italian researchers Dr. Graziella Pellegrini and Dr. Michele De Luca demonstrated for the first time that transplanting cultured corneal epithelium into such patients suppressed the invasion of the conjunctiva. J-TEC has introduced the techniques developed by Dr. Pellegrini and her team for the development of cultured corneal epithelium, as a contract development trusted by NIDEK Co, Ltd. Also, cultured oral mucosal epithelium was developed through the practical application of technology developed by Prof. Kohji Nishida of the Department of Ophthalmology, Osaka University Graduate School of Medicine.

製品化　Commercialization

自家培養角膜上皮（製品名：ネピック）は、2020年3月、眼科領域では国内初となる再生医療等製品として、角膜上皮幹細胞疲弊症（ただし、スティーヴンス・ジョンソン症候群、眼類天疱瘡、移植片対宿主病、虹彩症等の先天的に角膜上皮幹細胞に形成異常を来す疾患、再発翼状片、特発性の角膜上皮幹細胞疲弊症の患者を除く）を対象に国から承認されました。更に、2020年6月より保険が適用されています。
自家培養口腔粘膜上皮（製品名：オキュラル）は、2021年6月、眼科領域では第2号となる再生医療等製品として、角膜上皮幹細胞疲弊症を対象に国から承認されました。更に、2021年12月より保険が適用されています。

Autologous Cultured Corneal Epithelium (product name: Nepic) received approval in March 2020 from the Ministry of Health, Labor and Welfare for the indication of limbal stem cell dificiency (excluding diseases that cause congenital malformation of corneal epithelial stem cells such as Stevens-Johnson syndrome, ocular pemphigoid, graft-versus-host disease, iridosis, recurrent pterygium, idiopathic limbal stem cell dificienty), and has been listed as an item covered by the national health insurance since June 2020. Nepic is Japan's first regenerative medical product in the field of ophthalmology.
Autologous Cultured Oral Mucosal Epithelium (product name: Ocural) received approval in June 2021 for the indication of limbal stem cell dificiency as Japan's second regenerative medical product in the ophthalmology field, and has been listed as an item covered by the national health insurance since December 2021.

培養角膜上皮　開発者　Researchers

Michele De Luca, M.D.

再生医療における表皮幹細胞生物学の世界的権威。重症熱傷の治療のために欧州で初めて培養表皮幹細胞の移植を行った。
Modena and Reggio Emilia大学教授、イタリア

A world authority in the field of stratified epithelial stem cell biology, Prof. De Luca was the first person in Europe to carry out the transplantation of cultured epithelial stem cells. He is Professor of Biochemistry, Director of Center for Regenerative Medicine in the Department of Life Sciences, University of Modena and Reggio Emilia, Italy.

Graziella Pellegrini, Ph.D.

再生医療における角膜上皮幹細胞生物学の世界的権威。治療法の少なかった角膜欠損の治療を目的としたヒト角膜輪部幹細胞培養法を構築。
Modena and Reggio Emilia大学教授、イタリア

A world authority in the field of epithelial cornea stem cell biology, Prof. Pellegrini established the method of culturing human limbal stem cells for the restoration of damaged cornea incapable of repair through conventional treatment. She is Professor of Cell Biology, head of Cell Therapy Program of Center for Regenerative Medicine in the Department of Life Sciences, University of Modena and Reggio Emilia, Italy.

培養口腔粘膜上皮　開発者　Researchers

西田幸二 先生
Kohji Nishida, M.D., Ph.D.

自家培養口腔粘膜上皮およびiPS細胞を用いた培養角膜上皮等の開発者
眼科における再生医療の世界的権威
専門は脳神経感覚器外科学(眼科学)、再生医療
大阪大学大学院医学系研究科(脳神経感覚器外科学(眼科学)) 教授、日本

Developer of Autologous Cultured Oral Mucosal Epithelium, and Cultured Corneal Epithelium using iPS cells, etc. Global authority on regenerative medicine in ophthalmology.
Specializes in neural and sensory organ surgery (ophthalmology) and regenerative medicine.
Professor, Department of Neural and Sensory Organ Surgery (Ophthalmology),
Osaka University Graduate School of Medicine, Japan

CDMO・CRO
Contract Development & Manufacturing Service

再生医療等製品に関する開発製造受託サービス
Contract Development and Manufacturing Service for Regenerative Medical Products

蓄積されたノウハウと確立したシステムにより
開発初期から市販後まで、ワンストップかつシームレスなサービスを提供します。

Exploiting Our Accumulated Know-How and Established Systems,
We Offer One-Stop and Seamless Services from Initial Development to Post-Marketing.

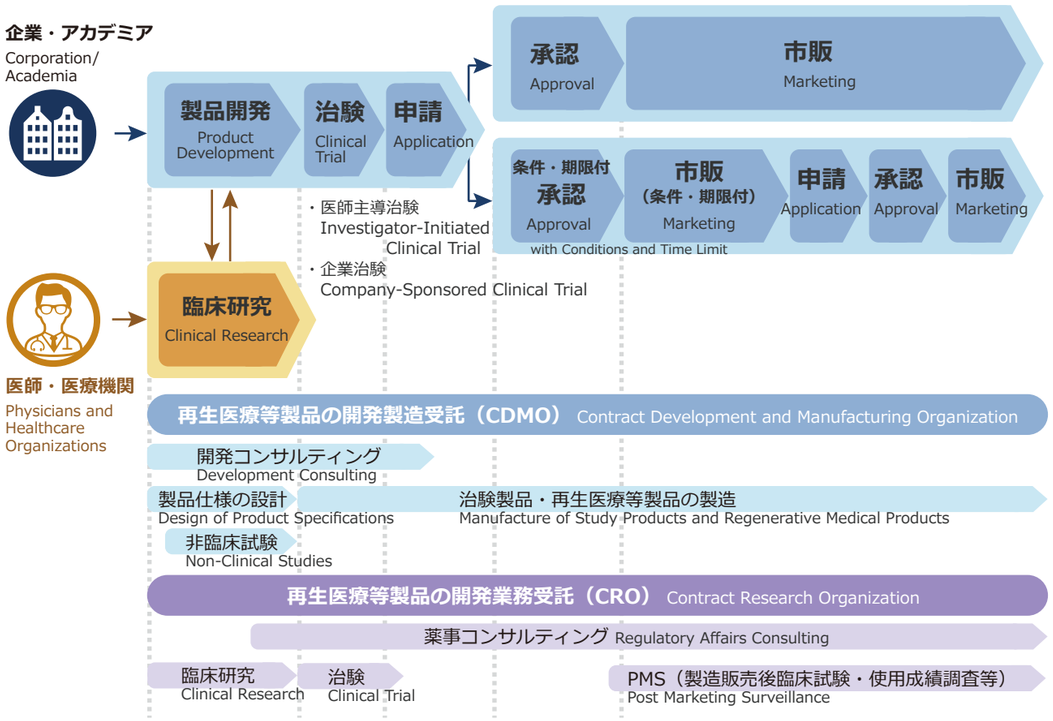
対象となる主な法規制：医薬品医療機器等法※
Main Applicable Law: The Pharmaceutical and Medical Device Act※

J-TECは、自社製品の開発で積み重ねた経験と、研究開発、臨床開発、薬事、生産、信頼性保証、営業などの再生医療等製品の開発・製造・販売に必要な組織体制を保有しています。蓄積したノウハウと確立したシステムにより、製品開発・製品製造を支援する再生医療等製品の開発製造受託（CDMO）および臨床試験などを支援する再生医療等製品の開発業務受託（CRO）の2つのサービスを提供し、お客様を開発初期段階から市販までシームレスに支援しています。

J-TEC has experience built on the development of our own products, as well as the organizational structure required for development, manufacture, and sales of regenerative medical products. This structure consists of research and development, clinical development, regulatory affairs, production, quality assurance, and sales divisions. Exploiting our accumulated know-how and established systems, we offer contract development and manufacturing (CDMO), and contract research (CRO) of regenerative medical products to support the development and marketing of our clients' products.

※医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律
The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

製品開発から市販までの流れと当社のサービス
The Flow from Development to Marketing of a Product and Our Service Menu



再生医療の提供（臨床研究・治療）への支援サービス
Supporting Service to Provide Regenerative Medicine (Clinical Studies and Treatment)

臨床研究の実施・治療の提供をトータルにサポートします。

We Offer Total Support for Clinical Studies and Treatment

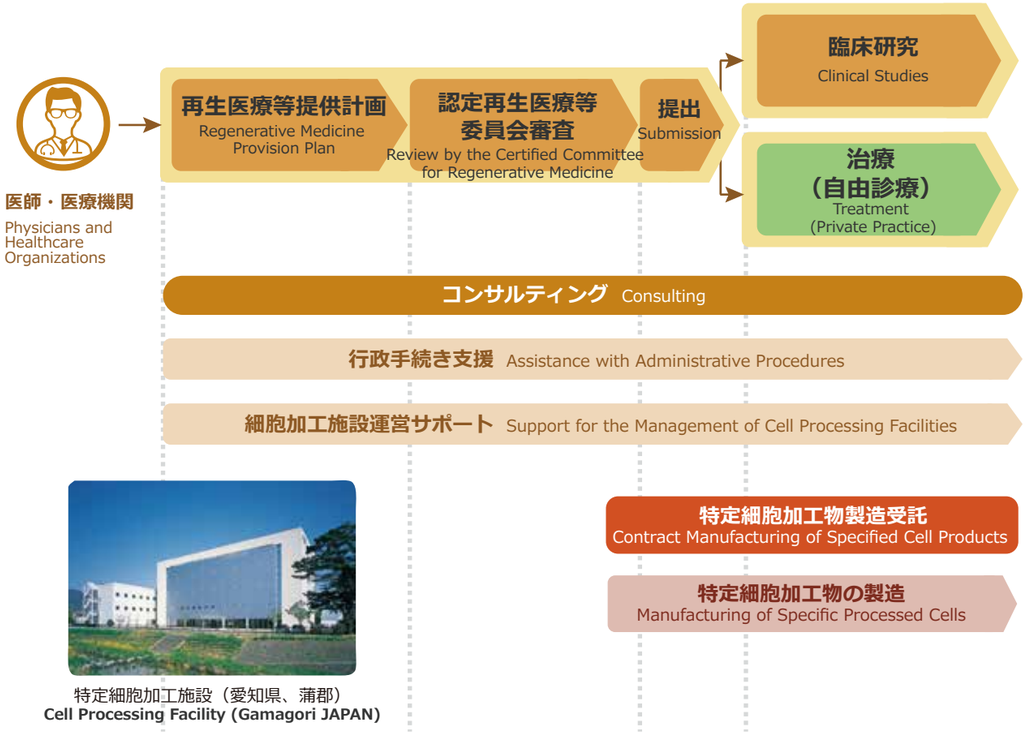
対象となる主な法規制：再生医療等安全性確保法※
Main Applicable Law: The Act on the Safety of Regenerative Medicine※

再生医療等安全性確保法の概要説明、再生医療等提供計画の作成および認定再生医療等委員会審査対応など、お客様の再生医療等に関する臨床研究の実施・治療の提供を、コンサルタントがトータルにサポートします。
また、医療機関の手順書（SOP）を基に、技術移管を行い、特定細胞加工物の製造を受託しています。当社の熟練した細胞培養技術者が細胞加工に関する技術を速やかに習得します。厚生労働省より許可を取得している当社の細胞培養加工施設で培養を受託することにより、迅速かつ効率的に製造を開始することができます。

Our consultant offers total support for clinical trials and treatment related to regenerative medicine, including explanation of the outline of the Act on the Safety of Regenerative Medicine, creation of a provision plan for regenerative medicine, and assistance with the review by the Certified Committee for Regenerative Medicine.
We transfer technologies and manufacture specified cell products for medical institutions based on their pre-established Standard Operating Procedures (SOP). Our experienced cell culture engineers will promptly master the technologies for cell processing. Approved by the Ministry of Health, Labour and Welfare, our cell culturing and processing facilities can start the culture services expeditiously and efficiently.

※再生医療等の安全性の確保等に関する法律
An Act on securing safety for regenerative medicine.

臨床研究、治療への流れと当社のサービス
The Flow from Plan Creation to Provision of Regenerative Medicine and Our Service Menu



特定細胞加工施設（愛知県、蒲郡）
Cell Processing Facility (Gamagori JAPAN)

研究用ヒト培養組織
Cultured Human Tissues for Research Use

治療用のみならず、医薬品や化粧品の研究用としても有用な
ティッシュ・エンジニアリング製品をお届けしています。

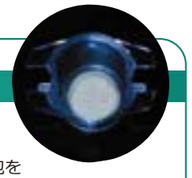
J-TEC offers human cellular and tissue-based products not only for medical applications but also for research on pharmaceutical and cosmetic products.

研究用ヒト培養組織とは　What are cultured human tissues for research use?

ヒトの細胞を用いて、体外で培養し再構築させた組織モデルのことです（製品名：ラボサイト）。ヒト組織にきわめて近い構造を再現できるため、動物や単純な培養細胞の代替となる種々の実験への適用が可能になります。J-TECは、医療用培養表皮や培養軟骨の開発で蓄積した高度な培養技術を有しています。この技術を研究用培養組織の開発に展開して、ヒト培養組織を用いた研究がさまざまな施設で実施可能となるように、多彩な製品開発を推進したいと考えています。

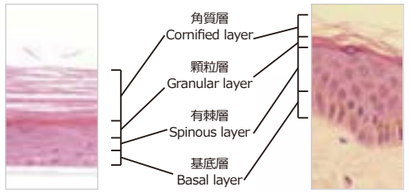
Cultured human tissues for research use (product name: LabCyte) are tissue models fabricated by culturing human cells in vitro. Because it is possible to reconstruct tissues with a structure extremely close to that of human tissue, they can be used to replace animals or simple cell cultures in a variety of experiments. J-TEC intends to use its high-level tissue culture technology to promote the development of a diverse range of human cellular and tissue-based products for research use and thereby encourage the implementation of research using cultured human tissues in a wide variety of facilities.

LabCyte EPI-MODEL



LabCyte EPI-MODEL（ラボサイト エピ・モデル）は、ヒトの表皮細胞を用いて製造した3次元培養表皮です。表面を空気に曝すことによって角質層を形成させており、ヒト表皮に類似した構造を構築しています。皮膚腐食性試験、皮膚刺激性試験、その他表皮を用いた各種研究に使用することができます。

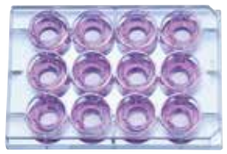
The LabCyte EPI-MODEL is a 3-dimensional cultured epidermis model that is reconstructed using human keratinocytes. The EPI-MODEL has a structure that is similar to that of the epidermis, and contains a cornified layer that is formed by culturing cells at the air-liquid interface. This model can be used as an alternative to animal experimentation, evaluation of chemicals by skin corrosion test and skin irritation test, and other epidermis-related studies.



LabCyte EPI-MODEL

ヒト正常皮膚
Normal human skin

監修：岐阜大学大学院医学系研究皮膚病態学　北島康雄先生
Data courtesy of Dr. Y. Kitajima (Gifu Univ.)



LabCyte EPI-MODEL

エピ・モデル24
皮膚刺激性試験法と皮膚腐食性試験法の
OECDテストガイドライン
（TG439・TG431）収載モデル
Skin irritation test method and skin corrosion test method using EPI-MODEL24 are included in the OECD test guideline (TG439, TG431).

LabCyte CORNEA-MODEL

LabCyte　CORNEA-MODEL（ラボサイト 角膜モデル）は、ヒト正常角膜上皮細胞を重層培養したヒト3次元培養角膜上皮です。物質の眼刺激性（＝安全性）を評価する方法として、動物を用いない試験法への強いニーズに応えるため、実際のヒト角膜上皮に類似した構造を持つ角膜モデルを開発しました。化合物の眼刺激性試験に加えて、角膜上皮の分子生物学的解析に使用することができます。

LabCyte CORNEA-MODEL is a 3-dimensional human stratified corneal epithelial model that has a structure similar to that of the corneal epithelium, and was developed to serve the strong need for an animal-free eye irritation test method. This model can be used for eye irritation tests of chemical compounds, as well as for molecular biological analysis of the corneal epithelium.

角膜モデル24
眼刺激性試験法のOECDテストガイドライン
（TG492）収載モデル
Eye irritation test method using CORNEA-MODEL24 is included in the OECD test guideline (TG492).

製品化への流れ
Value Chain

大切なのは「質と安全」。J-TECでは、各部門が役割を果たし、相互に協力しながら
高品質で安全な再生医療等製品を生み出しています。

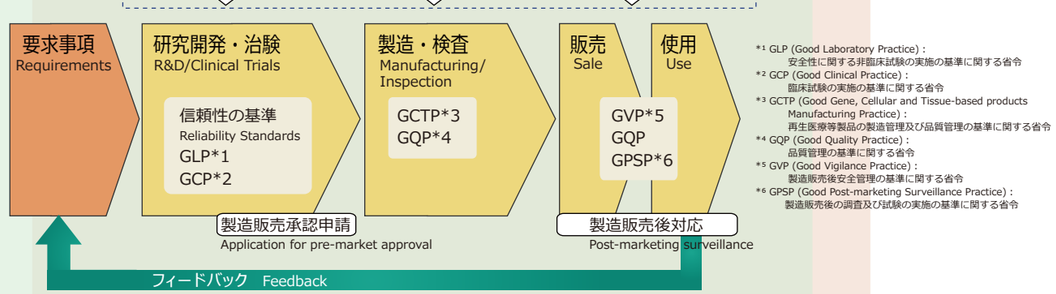
Quality and safety are our most important themes.
Staff of different departments is involved in the process of bringing regenerative medical products to patients.

『J-TEC品質方針』に基づいた活動　Putting J-TEC's quality policy into practice

J-TECは、製品の高い品質や有効性・安全性を科学的な根拠をもとに保証するだけでなく、医療関係者の方々や患者さまに製品を安定供給し、安心してご使用いただくことも社会的責任であると考えています。また、顧客の満足を得られるよう、質の高い優れた製品を適切な情報とともに提供しなければなりません。J-TECはこれらの要求事項を満たすため、品質マネジメントシステムを構築・運用し、「品質方針」を定め、業界のパイオニアとして責任ある事業を展開しています。

J-TEC believes that not only must we guarantee the high quality, efficacy and safety of our products based on scientific evidence, but we also have the social responsibility to ensure that patients and professionals in the medical field have a stable supply and can feel safe and comfortable using our products. Moreover, in order to satisfy our customers, it is imperative that we provide excellent, high quality products accompanied by appropriate information. In order to be able to satisfy these requirements, we are building and operating a quality management system, establishing a "Quality Policy", and as a pioneer in this field, growing and developing our business in a responsible manner.

品質マネジメントシステム　Quality management system



*1 GLP (Good Laboratory Practice)：
安全性に関する非臨床試験の実施の基準に関する省令
*2 GCP (Good Clinical Practice)：
臨床試験の実施の基準に関する省令
*3 GCTP (Good Gene, Cellular and Tissue-based products Manufacturing Practice)：
再生医療等製品の製造管理及び品質管理の基準に関する省令
*4 GQP (Good Quality Practice)：
品質管理の基準に関する省令
*5 GVP (Good Vigilance Practice)：
製造販売後安全管理の基準に関する省令
*6 GPSP (Good Post-marketing Surveillance Practice)：
製造販売後の調査及び試験の実施の基準に関する省令

J-TEC倫理基本方針 J-TEC's fundamental ethical policy

『J-TEC倫理基本方針』と倫理委員会　J-TEC's fundamental ethical policy and Ethics Committee

ヒト細胞・組織を用いた再生医療等製品の研究開発・製造は、十分な倫理的配慮の下に行わなければなりません。この考えに基づき、J-TECでは設立当初より倫理に関する基本方針を定め、ヒト細胞・組織の取り扱いに関してこの方針を遵守しています。その一環として、自社の倫理委員会を1999年に業界で初めて設置しました。このJ-TEC倫理委員会は、自社の委員だけでなく社外の専門家によって事業の倫理的妥当性を審議し、細胞・組織の収集・提供の実施状況および製品提供活動について客観的に監視します。

The research, development and manufacture of regenerative medical products using human cells and tissues can only be undertaken through the application of strict ethical principles. As the first company in the field, J-TEC has set a fundamental ethical policy since its foundation, and is commited to implement this policy in utilization of human cells and tissues. The Ethics Committee includes outside specialists, and debates the ethical appropriateness of the company's handling of human cells and tissues, and monitors the company's business activities.

生産体制
Production

細胞培養について熟知した専門家集団が細心の注意を払って製造に取り組んでいます。

The comprehensive knowledge of cell culture acquired by our specialist staff underlies their meticulous attention to detail in manufacturing.

再生医療等製品の有効性・安全性はヒトの生命に大きく関わるため、きわめて高品質な製品の製造が要求されます。J-TECでは再生医療等製品の製造管理及び品質管理の基準であるGCTP基準に準拠し、製造設備においては清浄空調設備や室圧管理システムによる環境管理、人・物の動線管理を行い、きわめてクリーンな環境を高水準に保っています。さらに、この環境下において、高品質で安定した製品を製造するために、細胞培養について十分訓練を受けた作業者が標準操作手順書に従って製造しています。
患者様からお預かりした組織で製造した再生医療等製品を、安全に確実に医療機関にお届けするために、このような対策を二重三重に講じ、製造を行っています。

As people's lives may depend on the efficacy and safety of regenerative medical products, their production must result in products of the highest possible quality. J-TEC complies with the GCTP for quality and manufacturing control of regenerative medical products. The environment within our production facilities is controlled by air conditioning and room pressure control systems, and the flow of people and objects is also controlled to maintain the environment in a highly clean state. Furthermore, to enable the production of high-quality, reliable products within this environment, production is carried out by operatives who are fully trained in cell culture techniques and who work according to standard operating procedures.
We have implemented this full range of safety measures to ensure that products cultured from patients' own tissue return to them safely and securely.

作業者：無塵衣・マスク・キャップ・手袋等を装着。細胞培養に関する専門的な知識を有し、再生医療等製品に特有な情報・培養技術に関して十分な教育訓練を受け、技能を確実に習得している者が従事

Operatives: All operatives wear appropriate uniforms in the production area. They have been fully trained and possess expertise on the cell culture techniques required for the production of regenerative medical products. Only personnel who have thoroughly mastered the necessary skills are engaged in the production.

クリーンルーム通路
Access corridor to clean rooms

安全キャビネット（共同開発品）：無菌操作のために、HEPAフィルター*を導入しクラス100*のクリーン環境を維持
Safety cabinet (jointly developed unit): A HEPA filter* has been installed and a Class 100* clean environment is maintained to enable sterile operations.

*HEPA（ヘパ）フィルター： High Efficiency Particulate Airフィルターの略。粒径0.3μmの微粒子を99.97%以上の集塵効率でキャッチし、空気を浄化するフィルター。クリーンルームや無菌操作時に必須。
*クラス100：一辺30.5cmの立方体中に0.5μm以上の微粒子が100個以下の非常に清浄な環境レベル。
*HEPA filter：A High Efficienty Particulate Air (HEPA) filter that purifies the air by removing particles of 0.3 μm or greater in diameter, with an efficiency of at least 99.97%. It is necessary for clean environment and sterile operations.
*Class 100: An extremely clean environment, with less than 100 particles of 0.5 μm or greater in diameter per cubic foot of air.

集中監視システム：空調・製造設備を24時間モニタリング
Centralized monitoring system: 24-hour monitoring of air conditioning and production facilities.

愛知県蒲郡市の本社工場（GCTP適合施設）
Headquarters in Gamagori city (GCTP compliant facility)

品質管理
Quality Control

安心を患者様へ。安全で健やかな細胞を患者様にお届けするために品質管理においても万全の体制を整えています。

To ensure that the cells we provide for patients are both safe and healthy, J-TEC has installed a thorough system of quality control.

再生医療等製品は患者様へ移植されることから、原材料の受け入れから製品の出荷までの行程を通して品質管理を厳重に行っています。

At every production stage, we carefully and consistently carry out strict quality control measures.

無菌性を保証するために行う各種試験は清浄度管理された室内で実施
Tests being carried out in the clean area.

原材料の管理　Raw materials/Animal-derived materials

製造に使用する原材料は、品質確保の観点から製造元を厳しく選定するとともに、受け入れ規格に適合した物のみを使用しています。動物由来の原材料については、感染症の問題から厚生労働省の示す生物由来原料基準を遵守し、安全性が確保された物を用いています。

Suppliers of raw materials are selected extremely carefully, and only raw materials that meet our stringent criteria are used in production. Animal-derived materials may only be used in compliance with the Standards for Biological Materials laid down by the MHLW, and if they have been ascertained to be safe.

製造環境の管理　Environmental cleanliness

製品を清浄な環境下で製造するために、定期的な清掃を徹底するとともに、浮遊微粒子数や環境微生物などのモニタリングを行っています。これらの管理作業により、清浄度の高い作業環境を維持しています。

To ensure and maintain cleanliness, not only is the production and testing area regularly and thoroughly cleaned, but it is also monitored for the number of airborne particles and environmental microorganisms.

教育訓練を定期的に受けた担当者が標準操作手順書を遵守して試験検査を実施
Trained personnel carry out quality control testing.

製品の品質試験　Quality control testing

安全で高品質な再生医療等製品を提供するために、製造工程中および出荷時の品質試験は、製品ごとに独自に開発した試験法や日本薬局方*等の標準化された手法で行われています。さらに細心の試験検査手法や機器を取り入れるよう検討を重ねています。試験検査業務は、専門知識を有し実務経験を積んだ担当者が、QMSに従い適切に管理された設備機器を用いて実施しています。

To ensure that J-TEC offers only safe, high-quality regenerative medical products, we carry out quality control tests according to both our own proprietary methods and standardized methods of the Japanese Pharmacopoeia* and other authorities. Testing operations are carried out by highly knowledgeable and experienced personnel in accordance with QMS, using appropriately managed facilities and equipment.

*日本薬局方：医薬品の性状および品質の適正を図るために厚生労働省が制定した規格基準書。品質を評価するための試験方法も記載。
*Japanese Pharmacopoeia: Regulations set out by the MHLW with the aim of ensuring that pharmaceutical products are adequate in terms of both properties and quality.

Research Use Only

Animal component free medium for human iPS/ES cells

Stem-Partner ACF

Animal component free and low protein content !!

- ○ High lot-to-lot consistency due to animal component free
- ○ This product containing less protein makes little interference with analysis of metabolites and proteome
- ○ Manufactured under GMP condition

Applicable cell lines

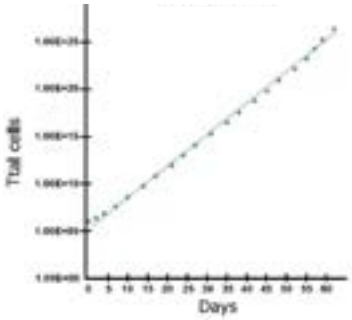
Human iPS cells	201B7, PFX#9
Human ES cells	H9, SEES2, SEES5

About Stem-Partner ACF

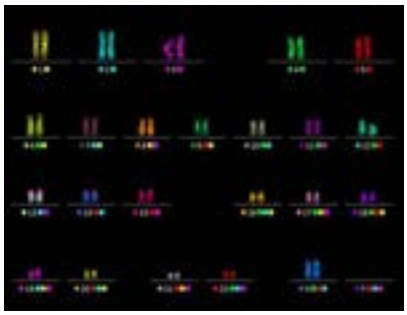
This product (animal component free) medium is to maintain undifferentiated state of human iPS/ES cells in feeder-free conditions. (Need to add bFGF)
Embryonic body can be formed in this medium without bFGF. It can be used not only for clump-cell culture but also single cell culture.

Data

A, Cell proliferation: hESC (H9)



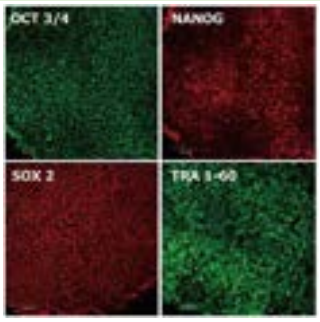
B, Karyotyping: hESC (H9), 17 passages



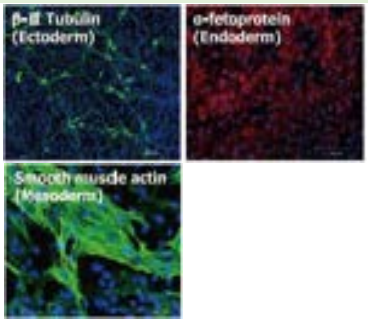
C, *CHD7* copy number of hESC (H9)

Methods		CHD7 copy numbers
on feeder	Small cell clumps	5220 (P29) 5100 (P36) 4900 (P38)
Stem-Partner ACF /VTN-N		4440 (P8)
Stem-Partner SF /VTN-N	Single cell suspention	3280 (P10)
Stem-Partner ACF /VTN-N		6040 (P18)

D, Immunostaining of pluripotency-related molecules



E, Immunostaining after embryoid body formation (*in vitro*)



F, Assessment teratoma formation (*in vivo*)

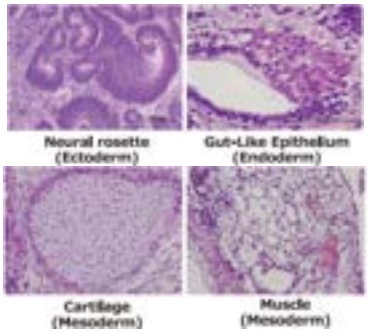


Figure A,B : The results of culturing hESC (H9) in undifferentiated state in this product (with VTN-N). Those cells showed high proliferative ability (A), and no chromosome abnormality (B). [unpublished data by Dr. Kawamata (FBRI)]
Table C : In comparison data of Stem-Partner ACF and SF for pluripotent stem cells, human ES cells maintained high copy number of CHD7 gene, which correlates differentiation potency. [Reference: "Yamamoto T., et al. *Scientific report*. 2018"]
Figure D, E, F : hESC (SEES2) was cultured in this product (with VTN-N). Those cells shown maintained undifferentiated state after passages (D), examined for their differentiation potential by embryoid body (EB) formation (E), and tissue section of teratoma, three germ layers of tissue were observed (F). [unpublished data by Dr. Umezawa (National center for Child Health and Development)]

Product name	Storage	Expiration date	Package	Price
Stem-Partner ACF	Under -15℃	12 months	500 mL	Contact us

KYOKUTO PHARMACEUTICAL INDUSTRIAL CO., LTD.

Cellular cryoprotectant

CP-1 High Grade

Cryoprotectant reagent for hematopoietic stem cells

- Over 25 years experience since 1992
- Enables cryopreservation using a -80℃ freezer
- More stable when stored in liquid nitrogen after freezing in a -80℃ freezer
- Enables cryopreservation of various cell lines
- Manufacured under GMP condition

※ This product is a reagent for *in vitro* research, and use of this product for medical treatment has not been approved.

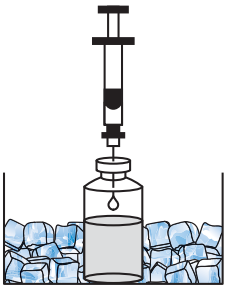
Cellular cryoprotectant「CP-1 High Grade」

This product has been commercialized as a cryoprotectant for hematopoietic stem cells. “CP-1 High Grade” enabled stable cryopreservation for a short period of time (6 months to 1 year and a half) using a -80℃ freezer without a program freezer.

Flowchart

CP-1
High Grade

	for 100 mL	for 50 mL
HES	12 g	6 g
DMSO	10 mL	5 mL
+Isotonic sodium chloride solution		
Total	68 mL	34 mL



Preparation method of CP-1 High Grade with HSA
As described below,
add HSA to CP-1 High Grade and mix.

for 100 mL : Add 32 mL of HSA
for 50 mL : Add 16 mL of HSA

HES	12%
DMSO	10%
HSA	8%

Preparation method of cell suspension
Prepare cell suspension with physiological saline (or RPMI1640 mediun).

The cell density to about 2×10^8 cells/mL

Equal volume mixture (on ice)

Final concentration

The cell density to about 1×10^8 cells/mL

HES	6%
DMSO	5%
HSA	4%

Rapidly store at −80℃

Store in −80℃ or less

Thaw rapidly in a warm water bath (37～40℃)

※Please read instruction carefully before using.

KYOKUTO PHARMACEUTICAL INDUSTRIAL CO., LTD.
7-8 Nihonbashi Kobuna-cho, Chuo-ku, Tokyo, 103-0024 JAPAN
Email cellculture@kyokutoseiyaku.co.jp Akiko Kawai (Ms.)

2023.12-01

Emerging Bio-medical Technology

MEDI NET

Corporate Profile

Feb. 2024

MEDINT Co., Ltd.

Corporate Profile

Philosophy

With the power of imagination, we turn creative vision into reality with the ethos of patient first.

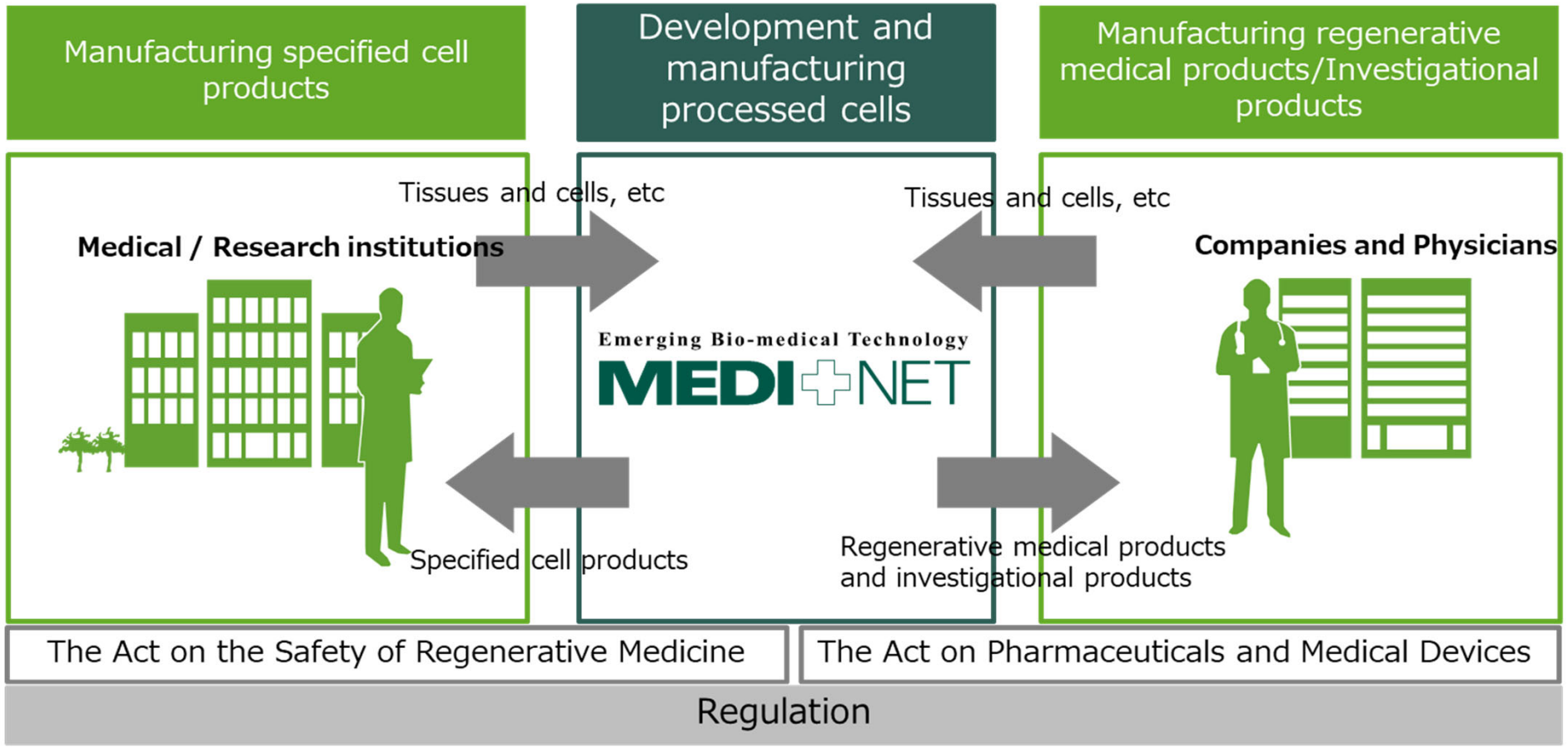
Mission

We create innovative technologies for building future medical care, and continue to bring such technologies to the public in a prompt and efficient manner.

Name	: MEDINET Co., Ltd.
Head Office	: Ota-ku, Tokyo
Date of Foundation	: October 17, 1995
Representative	: Representative Director of the Board and President Kanenao Kubushiro
Listed Market	: TSE Growth #2370
Paid in Capital	: JPY 5,736 Million (As of Sep. 30, 2023)
Number of Employees	: 98 (As of Sep. 30, 2023)
Business Segment	: Contract Cell Manufacturing Business Regenerative Medical Product Business

Business Segments

1. Contract Cell Manufacturing Business



2. Regenerative Medicinal Product Business

Development, manufacturing and sales of Regenerative medicinal products

Contract Cell Manufacturing Business

Shinagawa Cell Processing Facility

✓ **Gross Floor Area : 2990.5 m²**

Features

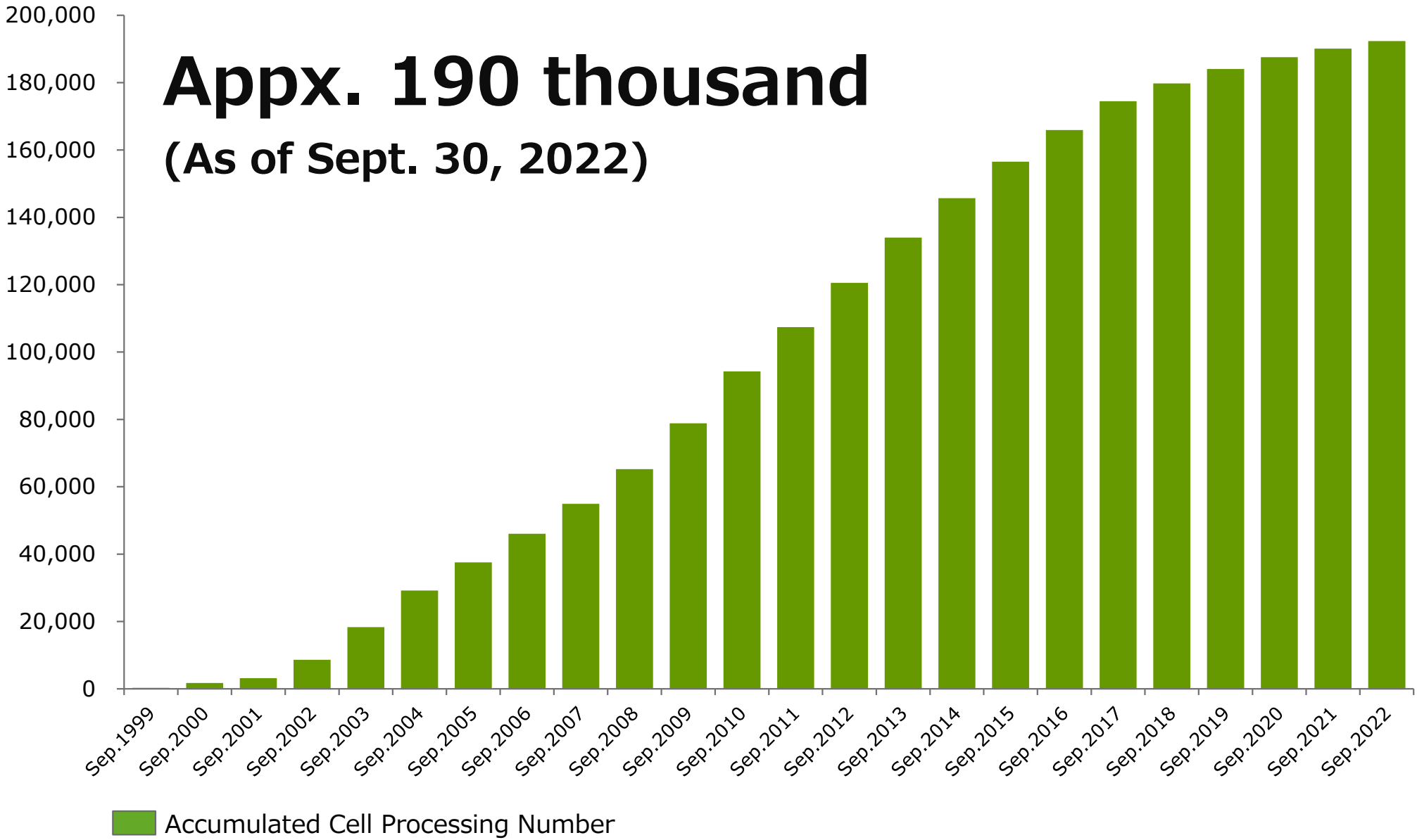
- Located 10mins. far from Haneda (Tokyo International) Airport
- Facility Structure for GCTP product
- Every kind of cells can be manufactured
- Gene transduction/transfection and a wide variety of test/examination can be conducted
- Place for product development and product manufacturing
- Obtained a license for manufacturing specified cell product (Registered facility number: FA3150001)
- Obtained a license for manufacturing regenerative medical product (License number: 13FZ110003)

MEDINET Technologies for Immuno-cell Therapy

NKT Cell Therapy (NKT cells-activated Dendritic Cell Therapy)	NKT cells, a type of lymphocyte that has the characteristics of both NK cells and T cells, are activated when presented with α-GalCer via dendritic cells. By returning α-GalCer-loaded dendritic cells to the patient's body, it is expected that NKT cells will be activated and proliferated in the patient's body.
Dendritic Cell Vaccine	Monocytes are isolated from peripheral blood of patient and are differentiated to DCs. Such DCs are cultured with proteins extracted from cancer cells or synthesized peptides (conjunctions of several to some dozen of amino acids,) which enables DCs to present antigens on their surface. Then DCs are reinfused to the patient. It is expected that those antigen-presenting cells induce tumor-specific T lymphocytes by presenting them to T-lymphocytes in-vivo.
NK Cell Therapy	Lymphocytes including αβT-cell, γδT-cell, NK cell, and other cells, are isolated from peripheral blood of a patient. Then selectively Activate and expand NK cells expressing CD16 and/or CD56 marker(s), which has high toxic activity to abnormal cells, with IL-2 and various stimulators outside of the patient's body and will be reinfused back to the patient.
γδ T Cell Therapy	Lymphocytes, including αβT-cell, γδT-cell, NK cell, and other cells, are isolated from peripheral blood of a patient. Such lymphocytes are selectively activated and expanded with mixture of aminobisphosphonate, Zoledronate, and IL-2 outside of patient's body, and then will be reinfused back to the patient.
αβ T Cell Therapy	Lymphocytes, including αβT-cell, γδT-cell, NK cell, and other cells, are isolated from peripheral blood of a patient. Such lymphocytes are activated and expanded with anti-CD3 antibodies and IL-2 outside of patient's body, and then are reinfused to the patient.

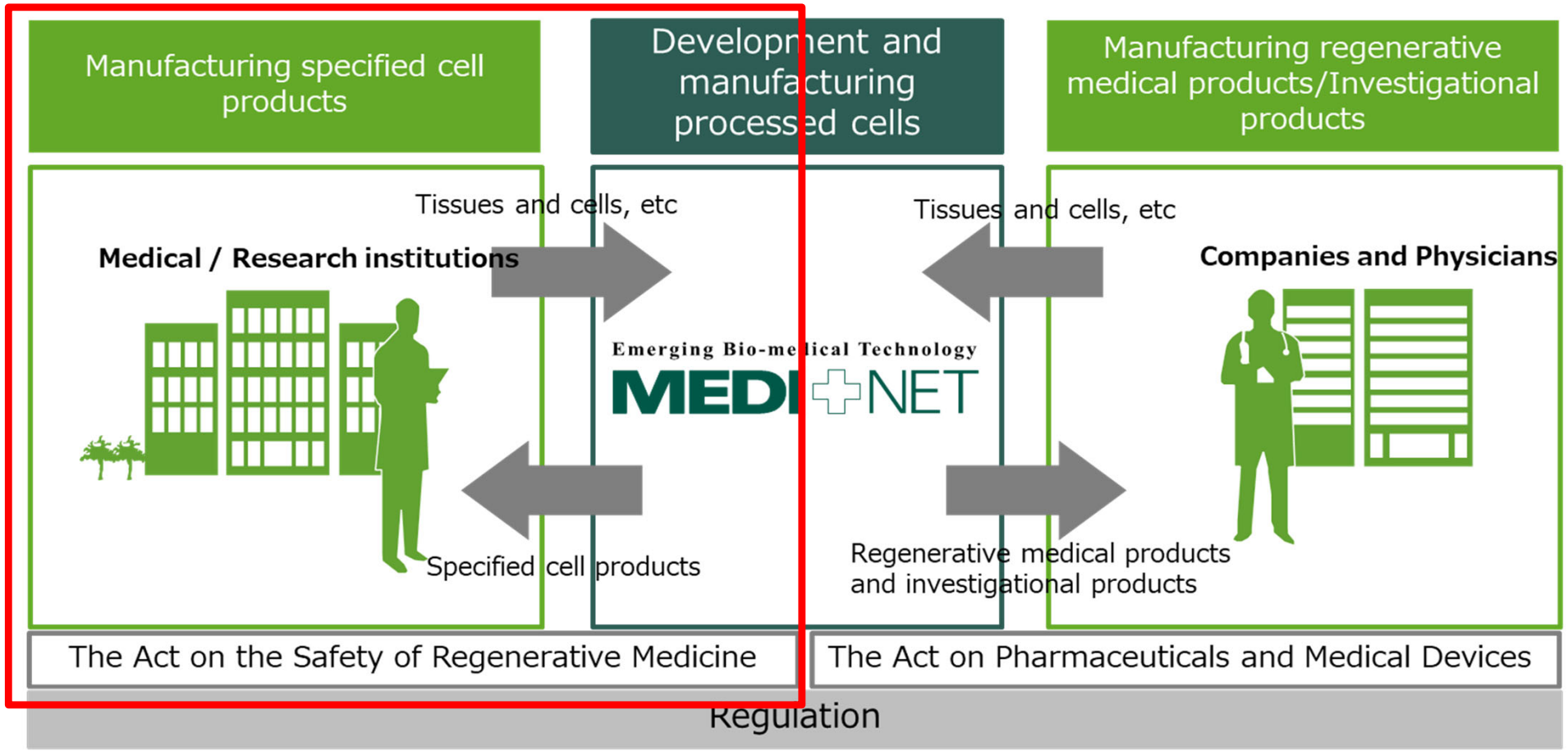
Activate, functionalize, and expand immune cells outside the body to treat cancers and viral infection (Treatment by autologous cells)

Cumulative Number of Cell Processing



Specified Cell Product Manufacturing Business

1. Contract Cell Manufacturing Business

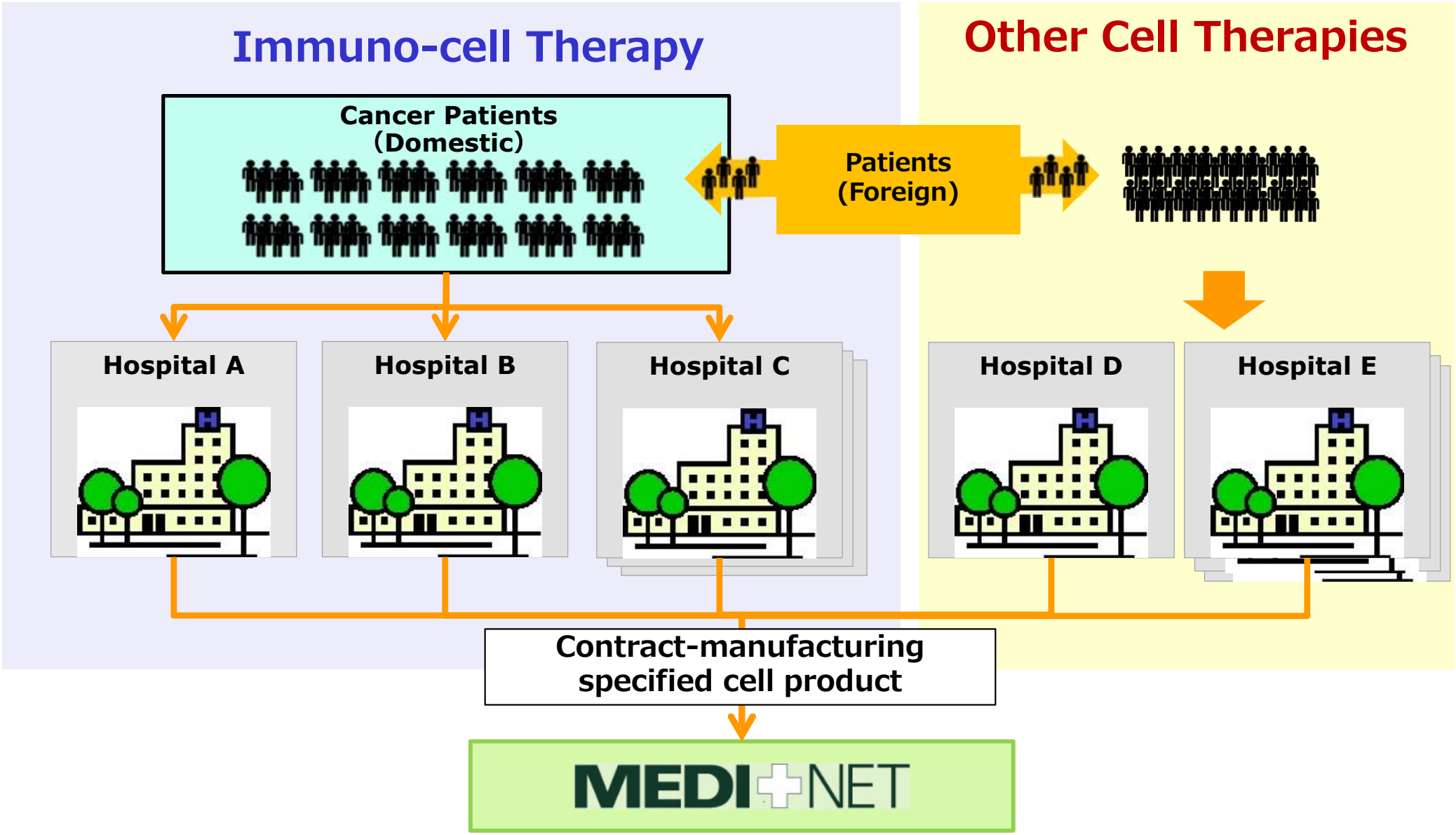


2. Regenerative Medicinal Product Business

Development, manufacturing and sales of Regenerative medicinal products

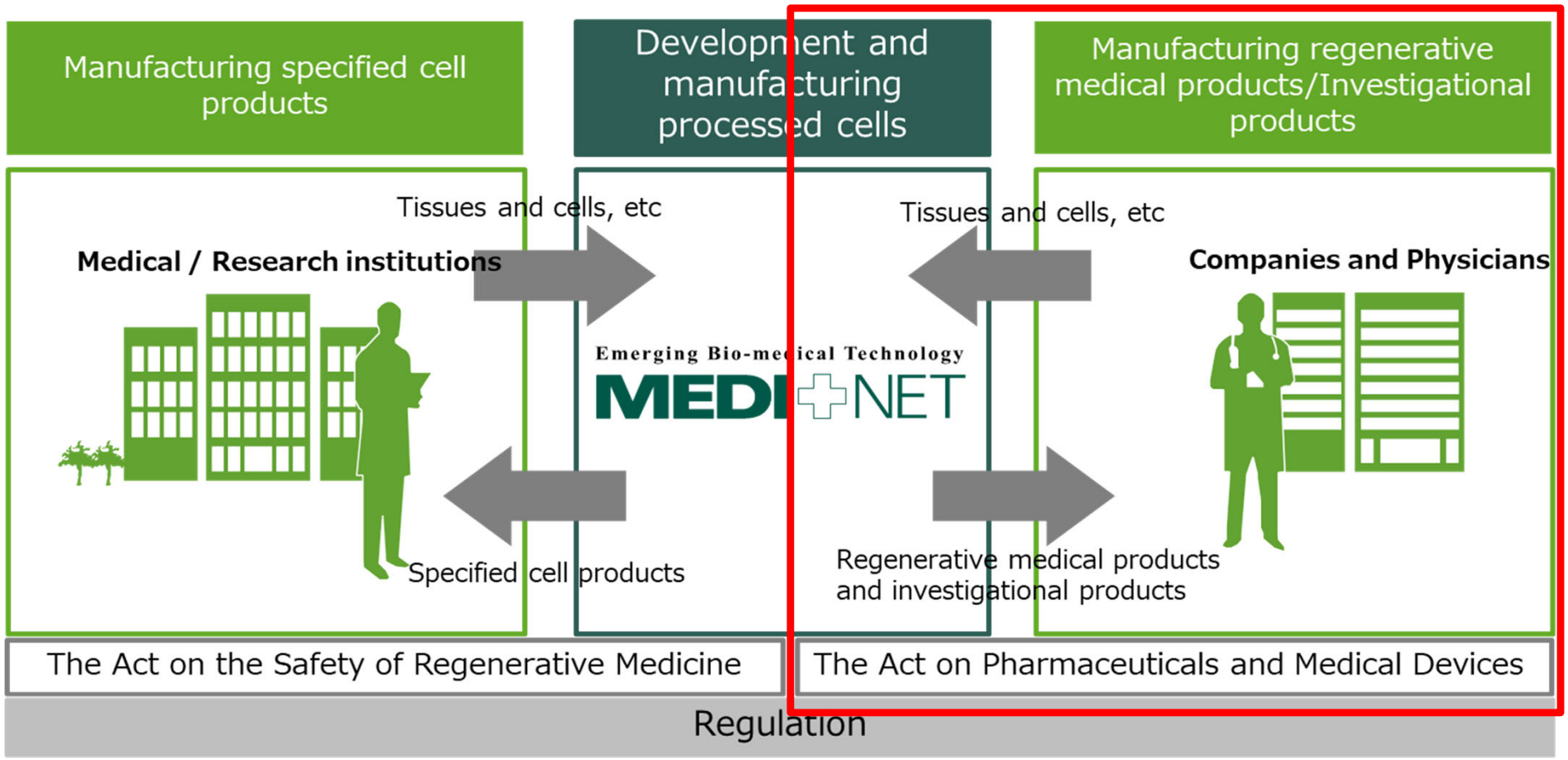
Specified Cell Product Manufacturing Business : Business Scheme

Contract Manufacturing for Medical Institution



CDMO Business

1. Contract Cell Manufacturing Business

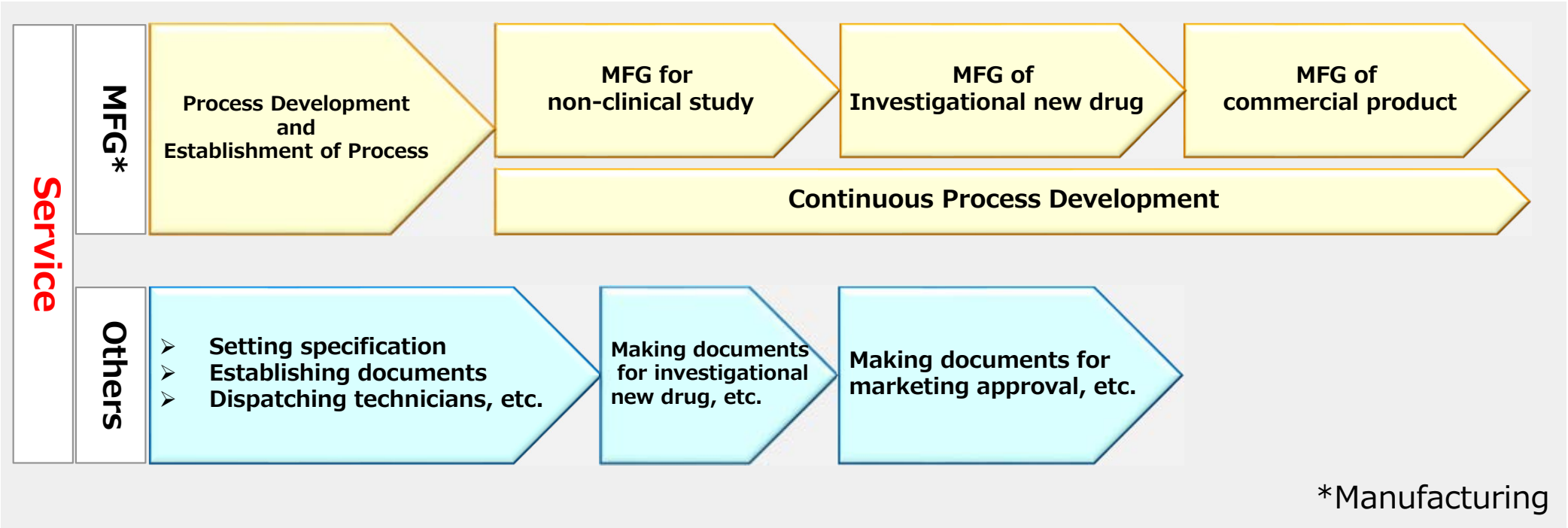


2. Regenerative Medicinal Product Business

Development, manufacturing and sales of Regenerative medicinal products

CDMO Business : Business Scheme

Contract Manufacturing and Development for Regenerative Medical Product



Truck Record (Excerpt)

- **Specified Cell Product Manufacturing Business**
  - ✓ Seta Clinic Tokyo
  - ✓ The University of Tokyo Hospital 22nd Century Medical and Research Center
  - ✓ Kyushu University
  - ✓ AOI Universal Hospital
  - ✓ Ibaraki Children's Hospital (Including development of cell processing technology)

- **CDMO Business**
  - ✓ Janssen Pharmaceutical K.K.

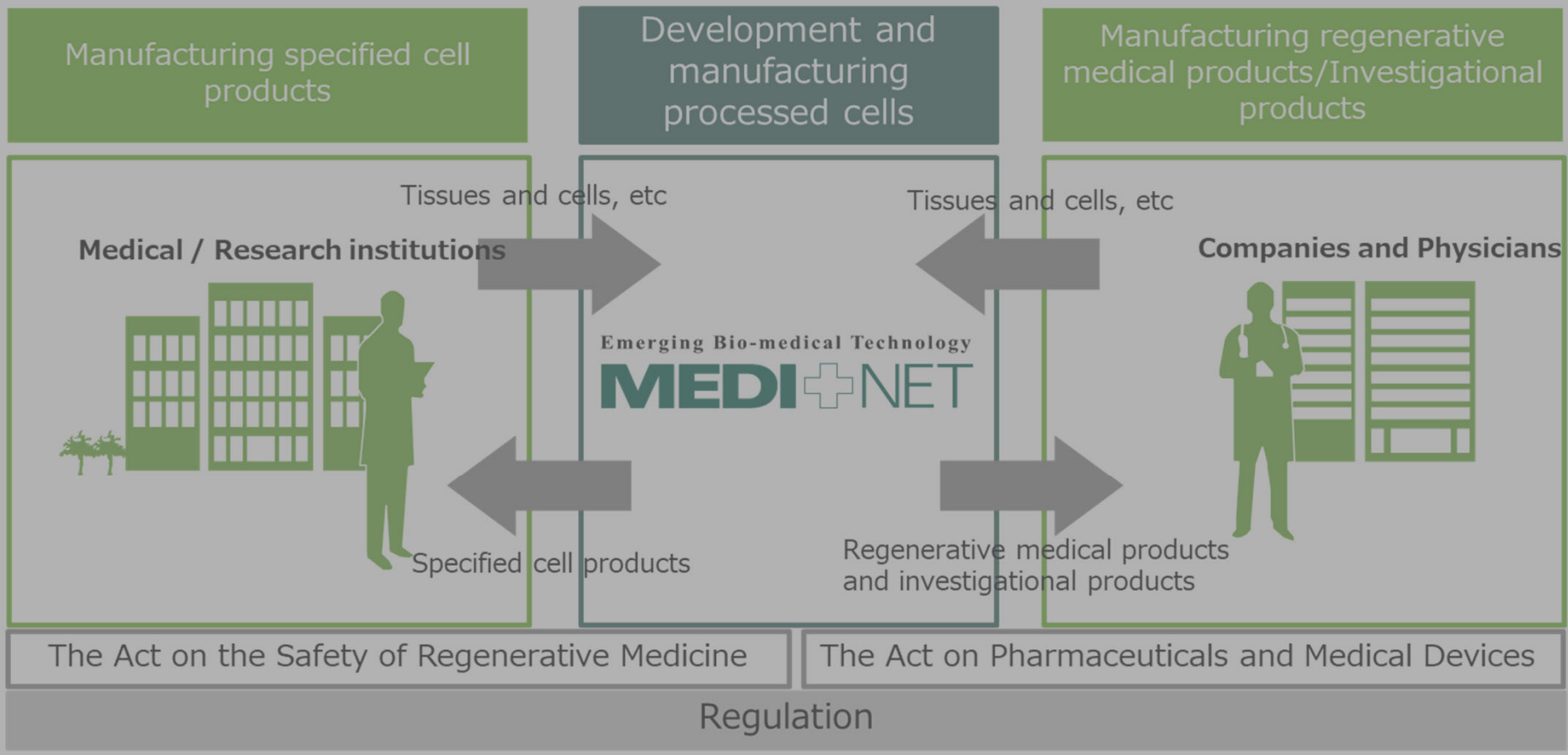
- **Value Chain Business**
  - ✓ Kanazawa University 【Facility Operation and Control】
  - ✓ Juntendo University 【Facility Operation and Control】
  - ✓ National Center for Child Health and Development 【Personnel Education】

- **Alliance**
  - ✓ CMIC Holdings 【Business Partnership】
  - ✓ Osaka National Hospital 【License out】
  - ✓ TC BioPharm (Scotland) 【License out】
  - ✓ EMO BIOMEDICINE (Taiwan) 【License out】
  - ✓ NK BIO (South Korea) 【License in】
  - ✓ MaxCyte (U.S) 【License in】
  - ✓ Medigen Biotechnology Corp. (Taiwan) 【License out】
  - ✓ CellAxia Inc. 【Business Partnership】

Regenerative Medical Product Business

Regenerative Medical Product Business

1. Contract Cell Manufacturing Business



2. Regenerative Medicinal Product Business

Development, manufacturing and sales of Regenerative medicinal products

Pipeline

As of Dec. 2022

Development Code etc.	Indication	Development Stage	Status
■Product Development			
MDNT01	Knee cartilage injury	PIII in the U.S by Histogenics Medavate Additional clinical trial for BLA Reconsider the development strategy in Japan	Ocugen (U.S company) and Medavate (U.S company) have signed an asset purchase agreement for autologous cell cultured cartilage, NeoCart, but due to the delay in asset transfer, MEDINET is currently requesting Ocugen to consider development promotion measurements for NeoCart.
■Research & Development			
Joint Research with National Cancer Center and Keio University	COVID-19 Preventive DC Vaccine		Manufacturing process and specification of the investigational new drug is currently being established. Also, preparation of phase I clinical trial is currently being carried out.
Joint Research with Kyushu University	Regenerative Medical Product for Chronic Heart Failure (αGalCer-DC)		Phase I/IIa clinical trial is completed. Currently, preparation of phase IIb clinical trial is being carried out in parallel with the discussion with PMDA.
Joint Research with National Cancer Center	Cancer Immuno-cell therapy using HSP105 Peptide		Under development.
2 Deoxyglucose Lymphocyte (2-DG)	Gastric Cancer		Preparation of non-clinical study is being carried out. The possibility of applying the technology to CAR-T is under consideration.
Joint Research with Kyoto Prefectural University	Removal of B cells for diseases caused by production of self-neutralizing antibody		Under development. PCT filed in Oct. 2020.
Joint Research with Seta Clinic	Immuno-cell therapy as preemptive medicine		Immune parameter is being established.

Sharing aspirations, innovating for tomorrow

MEDINET’S corporate brand statement reflects our commitment to fulfilling our mission and responsibilities toward society.

We links the hopes and aspirations of patients, their families, medical institutions, and enterprises, and in concert with them, realizes those hopes and aspirations with innovations for tomorrow.

Building on this approach, we will bring these innovations to people around the globe.
“Sharing aspirations, innovating for tomorrow”

We will keep pushing the limits of regenerative medicine and cell therapy, now and into the future.

Mitsui-Soko Group's Services for Regenerative Medicine

MITSUI-SOKO GROUP

◆ Storage and Transportation Services for Cells and Specimens

◆ Contract Logistics Services for Regenerative Medicine Products and Clinical Trial Products

Do you have any of these concerns?

Countermeasures for disasters	BCP for your valuable cells and products in the event of natural disasters such as earthquakes and hurricane
Reduction of workload	Heavy workload in daily logistics related management e.g. checking temperature, replenishing liquid nitrogen
Focus on core business	Difficulties in focusing on core task due to being taken up with registration and shipping arrangements
Securing storage space	Running out of warehouse space due to increase of inventory or SKU

Mitsui-Soko will solve your problems!

We provide safe and secured services based on our extensive logistics management expertise and large-scale facilities

Services

Storage

High quality operations in compliance with GMP and GCTP*

High quality control in cryogenic operations

[Storage in LN2 tank]

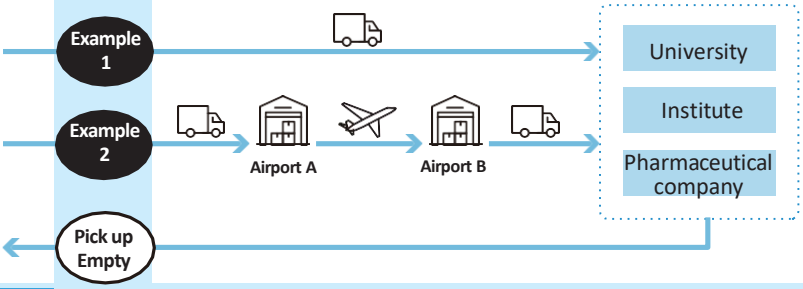
[Operations under LN2 gas phase]

[Maintenance and Records]
validation, periodic inspection, calibration, temperature controls, etc.

Distributions

Cryogenic transportation using in-house developed dry shipper

- **The best delivery arrangement by routes and temperature zones**
- **Development of standard operation procedures**
- **International deliveries also available**



Storage facility

Dedicated healthcare logistics facility
『P&M Center』

- Seismic isolation structure
- Back up generators
- Central air conditioning (2-8℃/15-25℃)

Required licenses obtained

Shipping Containers

Cryogenic transport container
『MEDiSTAR EX』

- Maintains below -60℃ for 168 hours
- Minimizing vibration
- Tracking temperature and vibration data

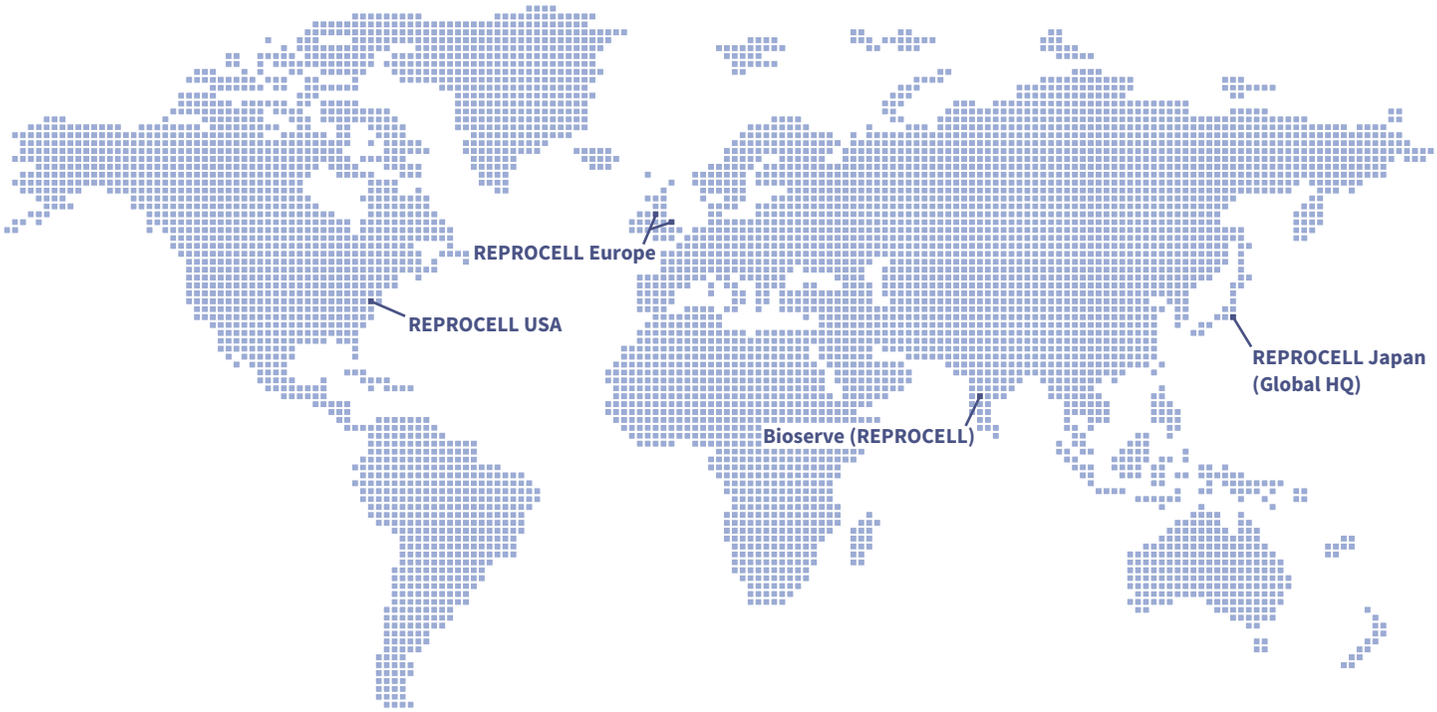
Air transportation available (including recording equipment)

*Good Gene, Cellular, and Tissue-based Products Manufacturing Practice in Japan regulation

Contact

Business Development Department, Mitsui-Soko Holdings, Co., Ltd.
3-20-1 Nishi-Shimbashi, Minato-ku, Tokyo 105-0003, Japan
E-mail: kenichi_kuchiki@mitsui-soko.co.jp, yuki_honda@mitsui-soko.co.jp

Our services and products for **stem cells** and **drug discovery** enable scientists worldwide to translate their research into clinical therapies.



REPROCELL USA

REPROCELL Europe (UK)

Bioserve Biotechnologies (India)

REPROCELL Japan (HQ)

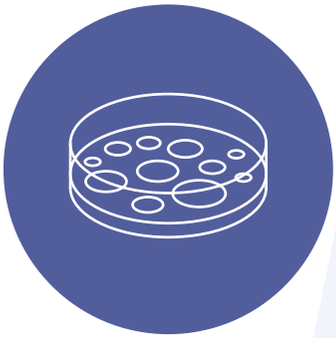
Established in 2003 by preeminent Japanese university researchers, REPROCELL quickly became the leading stem cell research company in Japan. Soon thereafter, REPROCELL products were employed by Professor Shinya Yamanaka during his pioneering research on iPSC technologies at Kyoto University. We were the first company to offer iPSC-derived human cardiomyocytes, hepatocytes, and neuronal cells for research applications and were listed on the Japan JASDAQ / Growth stock market in 2013.

Today, with expert scientists and laboratories on three continents, together with a number of service partners worldwide, REPROCELL provides a broad range of research and clinical stem cell services using our propietary RNA-based reprogramming technology; GMP iPSC master cell banks; MSC production and services for clinical applications; CRISPR-SNIPER gene editing services; a global biorepository of human tissue samples; preclinical genomic services; contract research preclinical assay services using human fresh tissue and bioengineered 3D tissue models; clinical central lab services; precision medicine services including our Pharmacology-AI machine learning platform; as well as an extensive product catalog of reagents, off-the-shelf iPSC cell lines, and labware for stem cell research and 3D cell culture.

reprocell.com

bioserve • stemgent • alvetex • biopta

REPROCELL's Drug Discovery and Analytical Services



Research Stem Cell Services

We have a complete portfolio of services for the reprogramming and differentiation of high-quality induced pluripotent stem cells (iPSCs). Our research stem cell services include donor recruitment, target cell isolation, iPSC reprogramming, expansion, characterization, neuronal differentiation, and gene editing. Using our proprietary RNA based technology, our services and products for stem cell scientists are used by leading pharmaceutical and biotechnology companies as well as top academic and government research institutions all around the world.

Clinical Stem Cell Services

With global access to clinical and commercially consented human tissue samples, we can procure the tissues needed for your cell therapy project and perform the necessary viral and donor profile screenings. Our experts use our own RNA based reprogramming technology to generate clinical iPSC Seed Clone Banks using clinical-grade media and reagents compliant with the regulatory standards and guidelines of the FDA, EMA, and PMDA. With our partner Histocell, we can provide clinical mesenchymal stem cells (MSCs) from your chosen donor or we can source one for you, all performed in compliancy with the regulatory standards. In addition, we can isolate GMP MSC derived secretosomes to move your project forward.

StemEdit Clinical Gene Editing Services

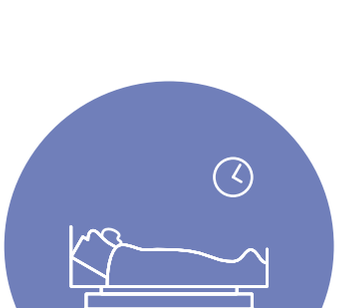
Through our collaboration with GenAhead Bio, we provide CRISPR-SNIPER clinical gene editing services. This novel approach to genome modification makes it possible to achieve otherwise challenging mutations such as the insertion of large gene fragments, biallelic mutations, and multiple gene knockouts — all with increased screening efficiency. CRISPR-SNIPER greatly increases the likelihood of project success. Our clinical gene editing service projects include bulk screening for optimal conditions, scheduled cloning, PCR confirmation of transfection and all required QC to ensure your clinically gene edited cells are suitable for cell therapy development.

Precision Medicine Services

Our precision medicine services include our new **Pharmacology-AI** machine learning platform. Developed in collaboration with IBM and STFC, our automated system rapidly identifies the features driving variation in patient outcomes — streamlining the development of effective patient stratification strategies. Scientists and clinicians with clinical or genomic data can use Pharmacology-AI to identify the key features driving biomarker levels, drug response, or clinical outcome. Our experts can enable IBD researchers to analyze their data via our platform to identify the key 'omic' or clinical features driving differences in drug or biomarker response. We are also developing applications for a number of other organ systems and therapeutic areas.

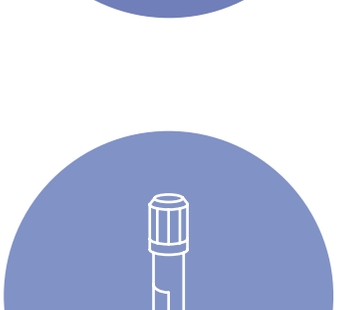
Preclinical and Drug Discovery CRO

Our GLP contract research services in human tissues have been trusted by the top pharma and biotech companies since 2002. We provide data that is highly predictive of *in vivo* drug responses by characterising drug safety, efficacy and absorption in human fresh tissues or bioengineered human tissues, de-risking later clinical trials. Through our extensive clinical networks in the USA and the UK, we have ready access to healthy and diseased human living tissues and organs. We also offer a range of assays in human bioengineered tissue models built on our Alvetex® platform, including models of IBD, skin and IPF, and can create custom assays for your drug discovery programs.



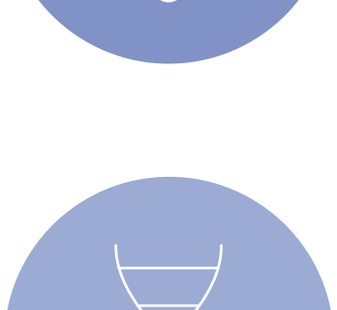
Clinical Laboratory Services

Our integrated network of central laboratories can support your clinical trial sample processing needs across three continents, from our accredited laboratories in the USA, UK, India, and Japan. Our GLP/GCLP and ISO compliant systems are operational 24/7. We offer a range of options including kit preparation, logistics, biospecimen processing and storage, biomarker discovery, and testing. We can coordinate, process, test, and analyze a range of fresh human biospecimens to meet the demands of your clinical research.



Human Tissue Samples

Our global biorepository of human tissue samples provides leading academic and industry researchers with access to over 600,000 human DNA, serum and tissue samples linked to detailed clinical and demographic data from 120,000 consented and anonymized patients on four continents. Customers of our human tissue samples and related molecular services include nearly every major pharmaceutical and biotechnology company, as well as top industry, academic, and government research institutions.



Genomic Services

We have more than two decades of experience in extracting DNA and RNA from a wide variety of starting materials. We have a large capacity to isolate different nucleic acids from a range of biospecimens, including blood, solid tissues, swabs, and formalin-fixed paraffin embedded blocks. Our preclinical genomic services include DNA and RNA extraction, biomarker discovery and validation, real-time PCR, and next generation sequencing.

REPROCELL Global

REPROCELL has aggressively expanded its business worldwide through a series of commercial acquisitions to become a global supplier and research partner for drug discovery, human tissue resources, and stem cell products for disease-model research.

In 2016, **REPROCELL USA** was established by merging the US holdings of Stemgent® Corporation (Lexington, MA) and Bioserve® Corporation (Beltsville, MD). A leader in iPSC reprogramming technologies, Stemgent is recognized for the brands of Stemolecule™ and StemFactor™, which are small-molecules and proteins for various stem cell and induced pluripotent stem cell (iPSC) applications that support growth and differentiation. Bioserve is a company with an extensive biobank of over half a million human tissue samples to support biomarker identification, and drug and disease research.

Also in 2016, **REPROCELL Europe** was established by merging the European holdings of Reinnervate® Corporation (County Durham, England) and Biopta® Corporation (Glasgow, Scotland). Known for the Alvetex® brand of plasticware plates and membrane products, Reinnervate developed 3D bio-engineered cell and tissue culture models. Biopta is a contract research organization (CRO) that specializes in customized drug discovery assays using live human tissues secured in accordance with government and medical agency ethical guidelines.

In 2018, REPROCELL acquired **Bioserve Biotechnologies India** Corporation (Hyderabad). Bioserve India offers a suite of services including oligo synthesis, DNA sequencing, and clinical oncology diagnostics. These services provide synergy with REPROCELL's stem cell technologies and innovative human tissue drug discovery services.

Working together as a global organization, REPROCELL provides an integrated workflow of services and products powering translational research with stem cells and discovery technologies for drug development and cutting-edge regenerative medicine. As a global technology partner, REPROCELL has the history, expertise, and flexibility to accelerate your research.

REPROCELL Brands

bioserve

Extensive biorepository of human tissue samples

Network of clinical sites for prospective sample collection

Molecular services

stemgent

RNA reprogramming systems and services

Reagents for pluripotent cell culture and differentiation

Extensive portfolio of small molecules

alvetex

3D cell culture technology creating *in vivo*-like cell environment

Protocols for stem cell, oncology and other tissue research applications

biopta

Experts in human tissue research services for drug development

Predictive safety, efficacy and ADME assays in human and animal tissues

REPROCELL

Improving human health through biomedical innovation and discovery

www.reprocell.com

Company Overview

REPROCELL was established in 2003 by preeminent Japanese university researchers, quickly becoming the leading stem cell research company in Japan. Soon thereafter, our products were employed by Professor Shinya Yamanaka (Nobel Laureate, 2012) for his pioneering development of induced pluripotent stem cells (iPSCs) at Kyoto University. We were the first company to offer iPSC-derived human cardiomyocytes, hepatocytes, and neuronal cells for research applications, and were listed on the JASDAQ (Japan) stock market in 2013.

To become a supplier and research partner for drug discovery, human tissue resources, and stem cell technologies, REPROCELL HQ (Yokohama, Japan) has since expanded through a series of commercial acquisitions. In 2016, the US holdings of Stemgent® Corporation (Lexington, MA) and Bioserve® Corporation (Beltsville, MD) were merged to form REPROCELL USA. As a leader in iPSC reprogramming technologies, Stemgent is recognized for developing the StemRNA™ Reprogramming Technology plus reagents to support the growth and differentiation of iPSCs. Bioserve is a company with an extensive biobank of over half a million human tissue samples to support biomarker identification, and drug research.

Also in 2016, REPROCELL Europe was established by merging the European holdings of Reinnervate® Corporation (County Durham, England) and Biopta® Corporation (Glasgow, Scotland). Reinnervate was known for the Alvetex™ brand of plasticware plates and membrane products, and for developing 3D models and applications for mammalian cell culture. Biopta is a contract research organization (CRO) that specializes in customized drug discovery assays using live human tissues secured in accordance with ethical guidelines .of governmental and medical agencies.

In 2018, the acquisition of Bioserve Biotechnologies India Corporation (Hyderabad) established Bioserve India, which offers DNA oligonucleotides and clinical diagnostic services in the areas of reproductive health and oncology. These services provide synergy with REPROCELL's stem cell technologies and innovative human tissue drug discovery services.

REPROCELL HQ
Yokohama, Japan
info-asia@reprocell.com

REPROCELL USA
Beltsville, MD
info-us@reprocell.com

REPROCELL Europe
Glasgow, UK
& Durham, UK
info-emea@reprocell.com

Bioserve
Hyderabad, India
salesindia@reprocell.com

Cover photo: the REPROCELL *Centre for Predictive Drug Discovery*, Glasgow UK.

REPROCELL provides products and services across the entire drug discovery process

TARGET IDENTIFICATION	TARGET VALIDATION	LEAD IDENTIFICATION	LEAD OPTIMIZATION	PRECLINICAL SAFETY	CLINICAL TRIALS
Over 600,000 human samples	Functional target validation in diseased tissues	Stem cells and 3D models as human relevant systems	Demonstrate efficacy in human fresh tissues	Detect adverse effects in human tissue and compare directly to animal data	Troubleshoot clinical observations in living human tissue
			Predict human absorption or metabolism		Clinical grade stem cell services and products

De-risking the discovery process by increased use of human data

REPROCELL has products and services that cover the entire drug discovery workflow. Human biospecimens can be obtained from partner organizations, reprogrammed by our RNA technologies into iPSCs, and cultured using our media and reagents. These iPSCs can be differentiated into various somatic cell types and grown using special scaffolds or culture-plates to create 3D model systems that more closely mimic real human tissue. And finally, these bioengineered human tissue models or living human tissues can then be used for preclinical drug development, or troubleshooting clinical adverse effects.

Pictures from REPROCELL Europe's *Centre for Predictive Drug Discovery* in Glasgow, UK.
From top right, clockwise: One of our researchers making full-thickness human skin biopsies; Alvetex Scaffold used to bioengineneer 3D human tissues: one of our researchers removing cells from a freezer.

Our human tissue specimens and molecular services can accelerate **Target Identification**

TARGET IDENTIFICATION | TARGET VALIDATION | LEAD IDENTIFICATION | LEAD OPTIMIZATION | PRECLINICAL SAFETY | CLINICAL TRIALS

Human Tissue Specimens

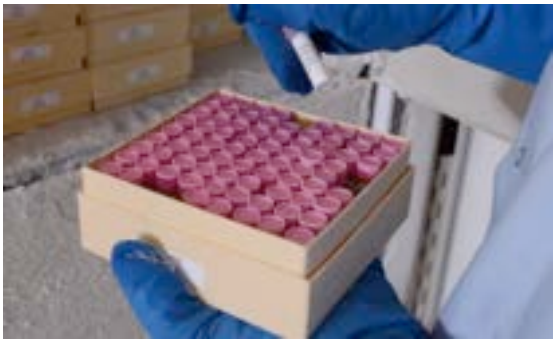
REPROCELL has one of the world's largest commercial biorepositories of human tissue samples, including over 600,000 samples of frozen tissue, FFPE tissue blocks, whole blood, serum, plasma, RNA and DNA samples. The samples in our collection are linked to detailed clinical and demographic data from over 120,000 consented and anonymized patients spanning four continents.

In addition, our network of partner organizations provides broader access to additional rare samples and the ability to source material specific to your research needs through prospective collections.

Global BioRepository Inventory by Disease Type

Cancers	**Metabolic**	**Miscellaneous**
Brain	Diabetes	Asthma
Breast	Cardiovascular	Pneumonia
Cervical		Dementia
Colon	**Metabolic**	Renal Disease
Head & Neck	Lupus	Hepatic Injury
Leukaemia / Lymphoma	Rheumatoid Arthritis	Osteoporosis
Lung	Multiple Sclerosis	Sepsis
Ovarian	Psoriasis	**Other**
Prostate	Rhumatoid Arthritis	Controls
Renal		

We have it... **Our network has it...** **Or, we can collect it**



Each human tissue sample is provided with:

- Detailed demographic information
- Gold standard clinical diagnostic information
- Complete drug history, including adverse events
- Full pathology report, including H&E slides
- Complete phenotypic data

Patient recruitment and tissue collection:

- Governed by IRB protocols and HIPAA regulations
- Ethically collected and broadly consented
- Sample data anonymized from original consents

Molecular Services

REPROCELL has a suite of preclinical molecular services for the identification of genetic markers, validation of drug targets and correlation of clinical and molecular data to accelerate the development of new and safer drugs.

With CLIA-approved laboratories and over 20 years of custom service experience, you can trust our quality and data accuracy.

REPROCELL iPSCs are ideally suited for applications in **Target Validation** and **Lead Identification**

TARGET IDENTIFICATION | TARGET VALIDATION | LEAD IDENTIFICATION | LEAD OPTIMIZATION | PRECLINICAL SAFETY | CLINICAL TRIALS

Cell Reprogramming Products

Our latest research-grade reprogramming technology, the StemRNA™ 3rd Gen Reprogramming Kit provides you with clinically relevant RNA iPSC lines.

Footprint-free and highly efficient, the StemRNA™ Reprogramming Technology is the only RNA methodology optimized on three different cell types (fibroblasts, blood-derived and urine-derived progenitor cells) and enhanced by both microRNAs and interferon-response suppression mRNAs.

The pluripotency potential, stability, and growth of iPSCs generated by the research-grade 3rd Gen StemRNA reprogramming technology is unrivalled and even uses an entirely xeno-free protocol for fibroblast reprogramming.

Top Products

StemRNA-3rd Gen Reprogramming Kit	00-0076
NutriStem® hPSC XF Medium*	01-0005
iMatrix-511 Stem Cell Culture Substrate*	NP892-11
NutriFreez D10 Cryopreservation Medium (50 mL)*	01-0020-50

*recommended for use with kit 00-0076

The StemRNA-3rd Gen Reprogramming Kit

Services for Reprogramming and Custom Primary Cell Derivation

REPROCELL can also source healthy or diseased skin, blood, or urine samples and derive target cell lines to generate iPSC lines. Multiple iPSC clones are genetically analyzed, validated for pluripotency, and profiled for donor authenticity.

In addition, our stem cell scientists can customize your service project based on your needs.

Our custom iPSC services use StemRNA™ Reprogramming Technologies which are available to both academic and industrial customers. For all research activities, use of the iPSCs are royalty-free.

Besides reprogramming, REPROCELL also offers services for expanding and differentiating your iPSC lines into various somatic cell types.

Our GMP iPSC Master Cell Bank manufacturing service can accelerate your journey from **Target Identification** to **Clinical Trials**

TARGET IDENTIFICATION | TARGET VALIDATION | LEAD IDENTIFICATION | LEAD OPTIMIZATION | PRECLINICAL SAFETY | CLINICAL TRIALS

GMP-grade Stem Cells

Our stem cell experts can manufacture GMP iPSC MCBs which are compliant with the regulatory standards and guidelines of FDA, EMA, and PMDA.

With global access to human tissue samples, we can procure the tissues needed for your cell therapeutic, perform the necessary viral and donor profile screenings, and derive the primary fibroblast culture. Using our propriety footprint-free RNA reprogramming technology, our stem cell experts can generate a clinically compliant iPSC seed stock using GMP-grade media and reagents. Clonal seed iPSC lines are available for evaluation by the client before committing to the MCB manufacturing step.

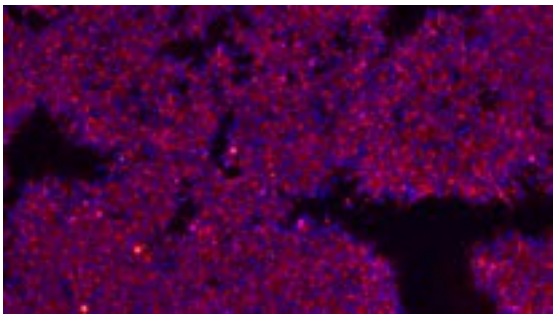
Under strict quality control measures, these seed iPSCs are expanded in a GMP environment to manufacture a Master Cell Bank. The final GMP iPSC lines are exclusive to the Sponsor; available only for your therapeutic project.

Alternatively, you can choose from our off-the-shelf seed stock iPSC lines.

Compliant with FDA, EMA, and PMDA

At REPROCELL, our GMP iPSC Master Cell Banks are manufactured in accordance with standards and guidelines of the three key regulatory agencies FDA, EMA, and PMDA.

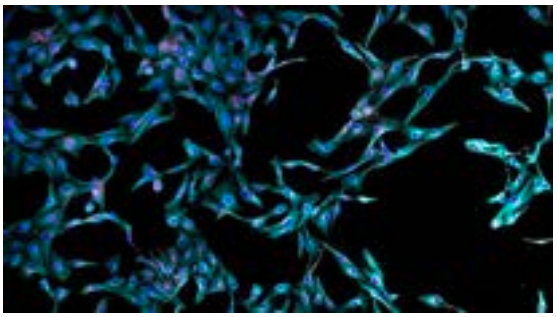
Our iPSC experts will provide the necessary quality and regulatory documents such as batch records, quality technical agreement, study reports, and COAs for your GMP iPSC MCB.



Commercial licence available

All our tissue donors have fully consented to clinical and commercial use.

REPROCELL provides the necessary clinical and commercial license for your project – making us a hassle-free one-stop solution provider for your clinical iPSC needs.



Our CRISPR-SNIPER gene editing service has a 97% success rate – even with challenging edits

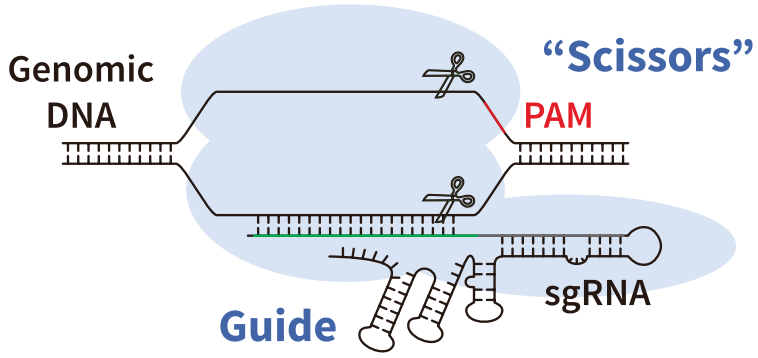
TARGET IDENTIFICATION | TARGET VALIDATION | LEAD IDENTIFICATION | LEAD OPTIMIZATION | PRECLINICAL SAFETY | CLINICAL TRIALS

CRISPR-SNIPER Gene Editing Service

In collaboration with GenAhead Bio, REPROCELL offers complementary state-of-the-art gene editing with our CRISPR-SNIPER Gene Editing Service.

CRISPR-SNIPER offers streamlined screening for positive results, resulting in high efficiency, high success rate editing. This service is ideal for challenging projects, such as creating single base changes, editing only one of a closely related set of genes, or isolating both homo- and hetero-allelic clones.

When combined with our custom tissue procurement and stem cell reprogramming in addition to differentiation services, genome editing provides concept-to-assay support for iPSC gene modification.



Comparison of Screening Methods

Condition	Positive Clones
SNIPER Screening	**20-30+%**
Traditional Screening	0.1-1%

REPROCELL's differentiated cell products, reagents and services are particularly useful to support research efforts in **Lead Optimization** and **Preclinical Safety**

TARGET IDENTIFICATION | TARGET VALIDATION | LEAD IDENTIFICATION | LEAD OPTIMIZATION | PRECLINICAL SAFETY | CLINICAL TRIALS

Stem Cell Culture Products

From our Dissociation Solution to ReproFF2 medium for feeder-free culture, REPROCELL original media are reliable and of high quality. For cultivation, dissociation, and freezing, we have a cell culture media right for you.

Top Culture Media Products

Dissociation Solution	RCHETP002
NutriStem® hPSC XF Medium*	01-0005
StemFit AKO2N (Japan only)	NP892-11
StemFit Basic O3 Medium	ASB03
StemFit Basic O4 Complete Type	ASB04CT
StemFit for MSC	AS-MSC
Primate ES Culture Medium	RCHEMD001

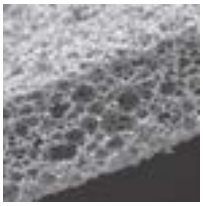
3D Cell Culture Products and Services

Technologies for cultivation of cells in 3D are becoming increasingly important in disease modelling, artificial organs, and drug discovery applications.

REPROCELL offers multiple 3D products and formats from which to choose. Alvetex™, REPROCELL's award-winning synthetic cell-culture scaffolds, are available in individual inserts, multiwell plates, or other configurations. EZSPERE® non-adherent microwell plates (Asahi Glass Company) promote formation of hundreds or thousands of aggregated cell spheroids.

For optimized iPSC suspension culture, the 3D Magnetic Stir and Disposable Bioreactor System (ABLE Corporation) is an outstanding option for growing 5 mL to 500 mL of batch cultures.

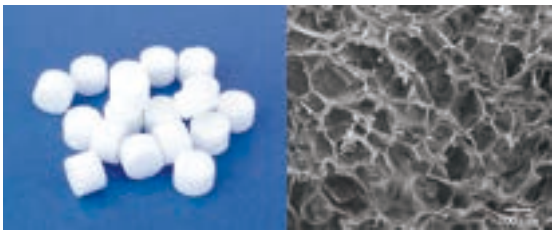
AteloCell® (Koken Pharma Corporation) is a cell culture scaffold made entirely from natural bovine collagen in the shape of discs and sponges.



Alvetex Scaffold membrane structure

Alvetex Scaffold 24 well insert

ABLE 500 mL Bioreactor



AteloCell sponges and scaffold structure

Cell culture applications are important in nearly all stages of drug development from **Target Validation** through **Preclinical Safety** assessment

TARGET IDENTIFICATION | TARGET VALIDATION | LEAD IDENTIFICATION | LEAD OPTIMIZATION | PRECLINICAL SAFETY | CLINICAL TRIALS

Cell Differentiation Products and Services

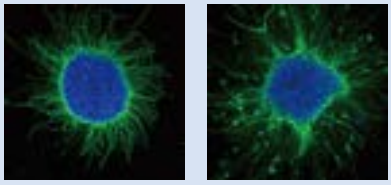
As a pioneering company in the production of iPSC-derived cells, REPROCELL has developed normal and disease-model cells (from patients with relevant diseases) of various types including neurons, hepatocytes, and cardiomyocytes. Our expertise and robust manufacturing processes ensure reproducible products and mature cell types that are electrophysiologically responsive.

REPROCELL's current stem cell product and service offerings are built around our proprietary Stemgent StemRNA™ 3rd Gen technology. This technology has been used to generate our StemRNA™ Neuro product line, of which Alzheimer disease model cells are also available. We also have a range of media and small molecules for stem cell research.

StemRNA™ Neuro – iPSC-derived Differentiated Neurons

REPROCELL's Stemgent StemRNA™ Neuro are differentiated iPSCs using proprietary technologies that result in a mixed population of neuronal cell types.

- World's first commercially available iPSC-derived human neurons
- Displays highly complex networked morphology with synaptic junctions
- Alzheimer disease options are available
- Clonally derived, highly consistent lot-to-lot performance, and stable phenotype



Outgrowth of Neurites from StemRNA Neuro cells (left) and StemRNA Neuro AD-Patient cells (right)

Reagents for Stem Cell Research

REPROCELL provides a single source of critical reagents for stem cell biology research. Each of our trusted brands is known for quality and consistency.

Our catalog of small molecules includes:

- GSK-3β inhibitors like CHIR99021
- Rho-kinase (ROCK) inhibitors like Y27632
- BMP inhibitors like LDN-193189

As well as many other Stemolecules™ for stem cell research. Our portfolio of Stemfactor™ cytokines and growth factors include basic FGF, LIF and Activin A.

Top Small Molecules

Stemolecule CHIR99021	04-0004
Stemolecule Y27632	04-0012
Stemolecule SB431542	04-0010
Stemolecule PD0325901	04-0006
Stemfactor FGF basic	03-0002
Stemfactor Human LIF	03-0016-100
Stemfactor Human Activin A	03-0001

REPROCELL provides products and services across the entire drug discovery process

TARGET IDENTIFICATION	TARGET VALIDATION	LEAD IDENTIFICATION	LEAD OPTIMIZATION	PRECLINICAL SAFETY	CLINICAL TRIALS
Over 600,000 human biospecimens from 120,000 donors	Functional target validation in disease tissues	Stem cells and 3D models as human relevant systems	Fresh tissue assays used to predict efficacy, absorption or metabolism	Detect adverse effects in human tissue and compare to animal data	Troubleshoot clinical observations in living human tissue

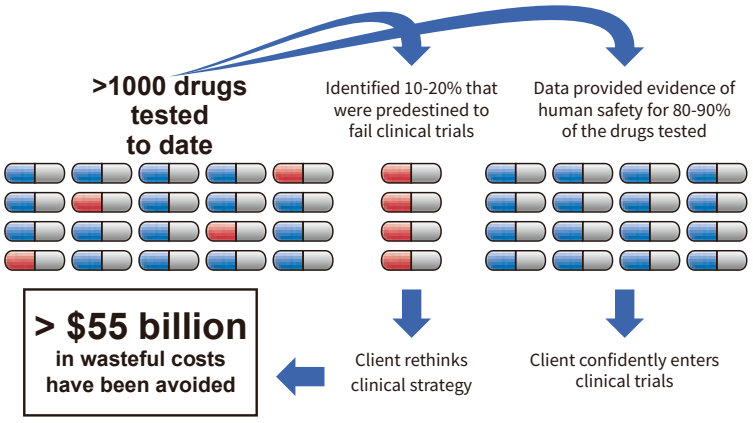
Drug Discovery Research Services

REPROCELL (previously Biopta) has been providing contract research services to the pharmaceutical industry since 2002 and has established itself as the world leader in the use of fresh functional human tissue research.

Our pharmacologists have a broad expertise in all areas of human tissue research, including sourcing, handling, and end point analysis. By predicting the safety, efficacy, absorption, or metabolism of compounds in phenotypically-relevant healthy and diseased human tissues, we generate data that can de-risk your drug development programs.

As owner of the industry's largest catalog of human functional tissue assays, we can customize experimental protocols to meet your specific needs. Having this insightful preclinical data early in discovery and development will help you to reduce the number of compounds that fail in the later stages; we estimate that since our establishment, we have helped Pharma save over $55 billion research dollars.

REPROCELL's human tissue technology predicts clinical success by using the closest possible model of drug behavior in humans



Lab Testing Capabilities include:

- IBD
- Skin Disease
- ADME DMPK Assays
- Gastrointestinal Motility
- Species Comparisons
- Cardiovascular
- Respiratory
- Genitourinary
- Neuronal

Improving human health through biomedical innovation and discovery

bioserve

- Extensive biorepository of human tissue samples
- Network of clinical sites for prospective sample collection
- Molecular services

stemgent

- RNA reprogramming systems and services
- Reagents for pluripotent cell culture and differentiation
- Extensive portfolio of small molecules

alvetex

- 3D cell culture technology creating *in vivo*-like cell environment
- Protocols for stem cell, oncology and other tissue research applications

biopta

- Experts in human tissue research services for drug development
- Predictive safety, efficacy and ADME assays in human and animal tissues

Improving human health through
biomedical innovation and discovery

https://www.reprocell.com/contact

Stem Cell Services for Cell Therapy Manufacturing

stemgent
A REPROCELL BRAND

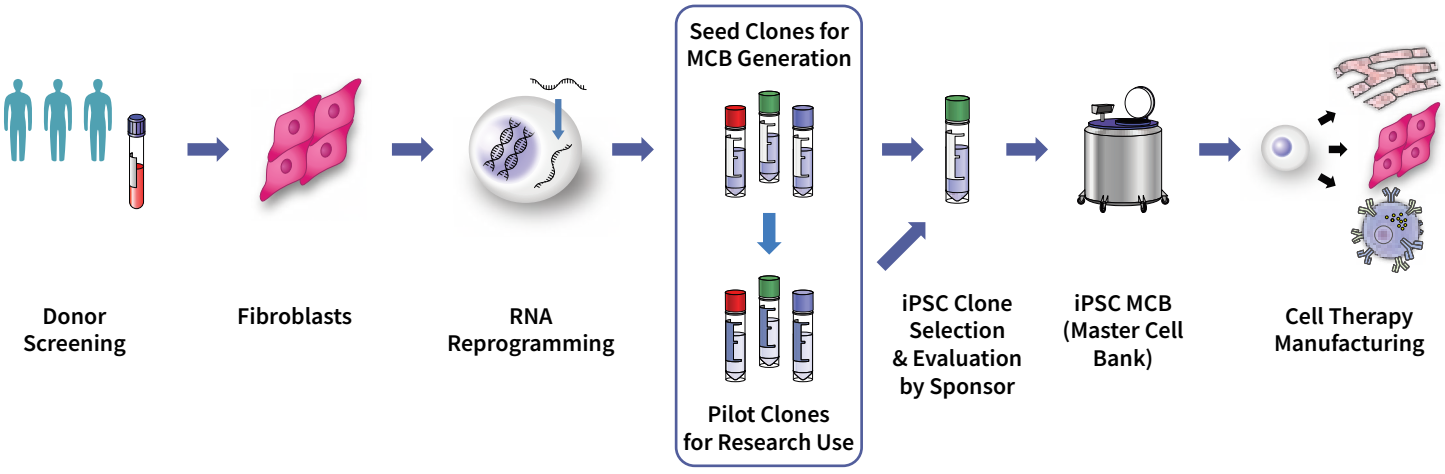
Regulatory compliant iPSCs

As a partner for your clinical cell therapy project, REPROCELL creates **StemRNA™ Clinical iPSC Seed Clones**. From a clone evaluated and selected by the Sponsor, we will first manufacture a GMP Master Cell Bank (MCB) that is compliant with the current standards outlined by the key regulatory agencies in the US, Europe, and Japan (FDA, EMA, PMDA) and eligible for downstream processing into a cell therapy product. We are committed to advancing your regenerative medicine project by providing all necessary quality and regulatory documents.

Your GMP partner

- **Footprint-free RNA reprogramming**
- **Ready-to-use and custom iPSC services**
- **Unique evaluation of Clinical iPSCs**
- **Comprehensive end-to-end clinical services**
- **Cell Therapy Manufacturing**
- **Clinical Gene Editing**
- **Simple commercial license**

Our Clinical Stem Cell Project Workflow



REPROCELL's process starts with skin biopsies from carefully screened and ethically consented donors. Fibroblasts isolated from these biopsies are reprogrammed into Seed iPSC Clones using our clinical StemRNA 4th Gen Reprogramming Technology. These iPSC Clones can be evaluated by the Sponsor to select a suitable clone for GMP MCB generation and down-stream Cell Therapy Manufacturing. From our bank of Seed Clones, we manufacture corresponding Pilot Clones which are suitable for research use to develop and evaluate your own protocols. The entire clinical process complies with regulations of the US FDA, European EMA, and Japanese PMDA.

REPROCELL
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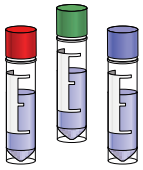
Three Ways to Access iPSC Clones

- We can create ***exclusive* StemRNA Clinical Seed Clones** for you starting with a donor that matches your criteria.
- We also have a bank of ***ready-to-use* StemRNA Clinical iPSC Seed Clones** for your evaluation.
- We have also created corresponding **StemRNA Clinical iPSC Pilot Clones** from these Seed Clones.

The difference between Seed and Pilot Clones

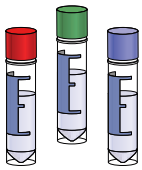


StemRNA Clinical iPSC Seed Clones

These cells are suitable for clinical use through subsequent regulated and approved processes, including processes resulting in a GMP Master Cell Bank and Working Cell Bank. StemRNA Clinical iPSC Seed Clones are generated under CGTP guidelines and covered by a rigorous quality control (QC) process that is compliant with US FDA, European EMA and Japanese PMDA regulations.

StemRNA Clinical iPSC Pilot Clones

Our non-exclusive *ready-to-use* iPSC Pilot Clones are directly expanded from our bank of StemRNA Clinical iPSC Seed Clones in a research setting. These clones are NOT suitable for development for clinical use and are for evaluation purposes only, but they provide a more cost-effective way to access StemRNA Clinical iPSCs to develop and evaluate your process.

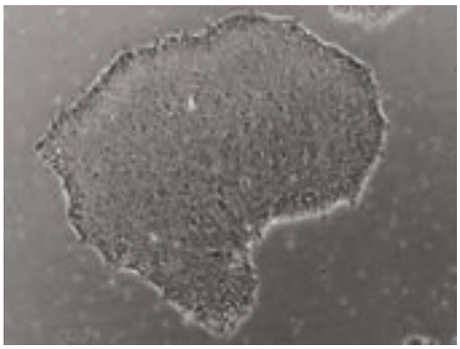


The Advantages of the StemRNA Clinical Approach

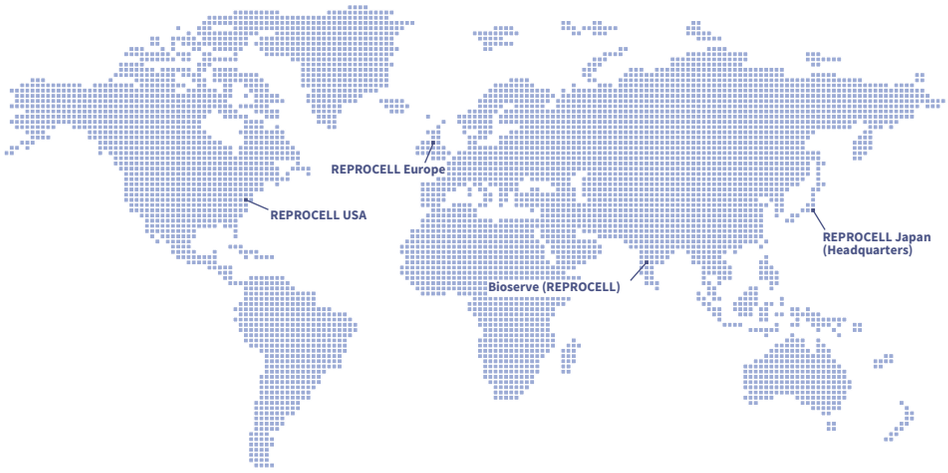
- **Every step in the manufacturing process is covered by extensive QC to ensure compliance with FDA, EMA, and PMDA regulations**
  — Minimizes the Sponsor's risk of downstream obstacles
- **Reprogramming process uses the latest generation of clinical RNA reprogramming technology**
  — Eliminates risks associated with retention of reprogramming vectors
- **Evaluation period allows the Sponsor to pick the best clone for continuing with GMP manufacturing**
  — Ensures the suitability of the right iPSC clone
- **GMP compliant MCB and Cell Therapy manufacturing performed by experienced scientist in ISO certified clean rooms using high-quality procedures and systems**
  — Minimizes the risk of human error and environmental contamination
- **Pilot Clones provide a cost-effective tool for method development and research, while providing access to clinically-compatible clones for GMP manufacturing**
  — Minimizes the financial risk during the research and method development phase

Find out more: **www.reprocell.com/clinical-stem-cell-services**

Research Stem Cell Services



REPROCELL has labs across the globe to support your stem cell project



REPROCELL USA
Beltsville, Maryland

REPROCELL Europe
Glasgow, Scotland

Bioserve (India)
A REPROCELL Group company

REPROCELL Japan
Global headquarters

Let us do the work for you

Our experts are available to reprogram primary cells for you – giving you more time to focus on your research. Every REPROCELL service project is milestone-based and customizable to meet your needs, with a dedicated study director to keep you updated throughout the duration of your project.

Why work with REPROCELL?

- **The StemRNA Reprogramming Technology**
  RNA reprogramming provides the most rapid, highest quality iPSCs of any commonly used reprogramming method.
- **Our Experienced Staff**
  Our staff has more than 100 years' combined experience in some of the most well-known stem cell labs.
- **Our Dedication to Quality**
  Our quality control regime is custom-tailored to provide you with the assurance you require.
- **Our Access to Starting Cell**
  The REPROCELL Tissue Network can provide starting cells from donors that match your profile.
- **Our Differentiation Experience**
  Our scientists have expertise in iPSC differentiation to a variety of cell types to provide you the cell types you need.

Our Quality Control process can be customized to meet your needs, including karyotyping, immunostaining for pluripotency, trilineage differentiation and any other assays you require.

Table: Standard quality control on iPSCs.

Test	Method
Microbiology	Mycoplasma, Sterility, Virology
STR Genotyping	CellCheck 16 Plus
Morphology	Quality and Differentiation Scoring by Phase Contrast Microscopic Observation
Cell Viability and Growth Rate	Trypan Blue staining
Karyotype Analysis	G-band analysis
Pluripotency Analysis	Immunofluorescence, Flow Cytometry, Directed Differentiation

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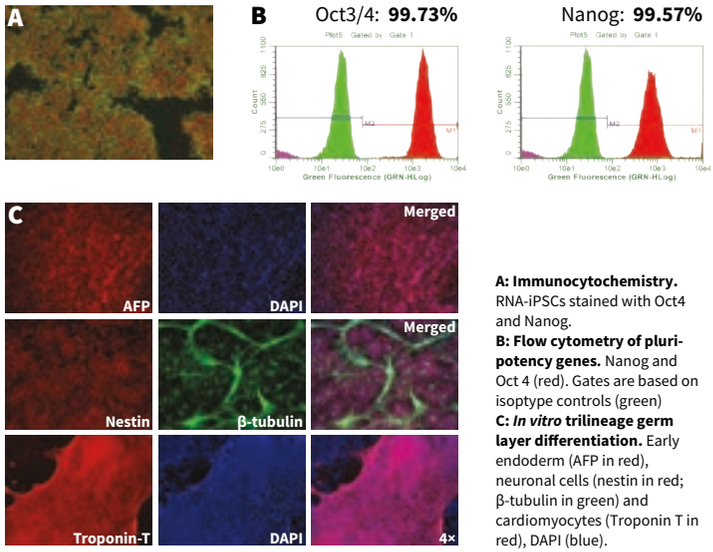
Key Benefits of StemRNA Reprogramming

- **Flexible reprogramming technology generates high quality human iPSC lines from multiple target cell types**
  The StemRNA 3rd Gen Reprogramming Technology supports the generation of iPSCs from multiple donor cell types (fibroblasts, urine cells, etc.)
- **High efficiency, non-integrating reprogramming**
  StemRNA-3rd Gen creates iPSCs with high efficiency which facilitates reprogramming of difficult to reprogram samples, such as high-passage number or older donors.
- **Time-saving protocol delivers faster results facilitating higher throughput**
  No retention of reprogramming vectors means that screening iPSCs for vector retention is unnecessary.

RNA Reprogramming yields high quality iPSCs

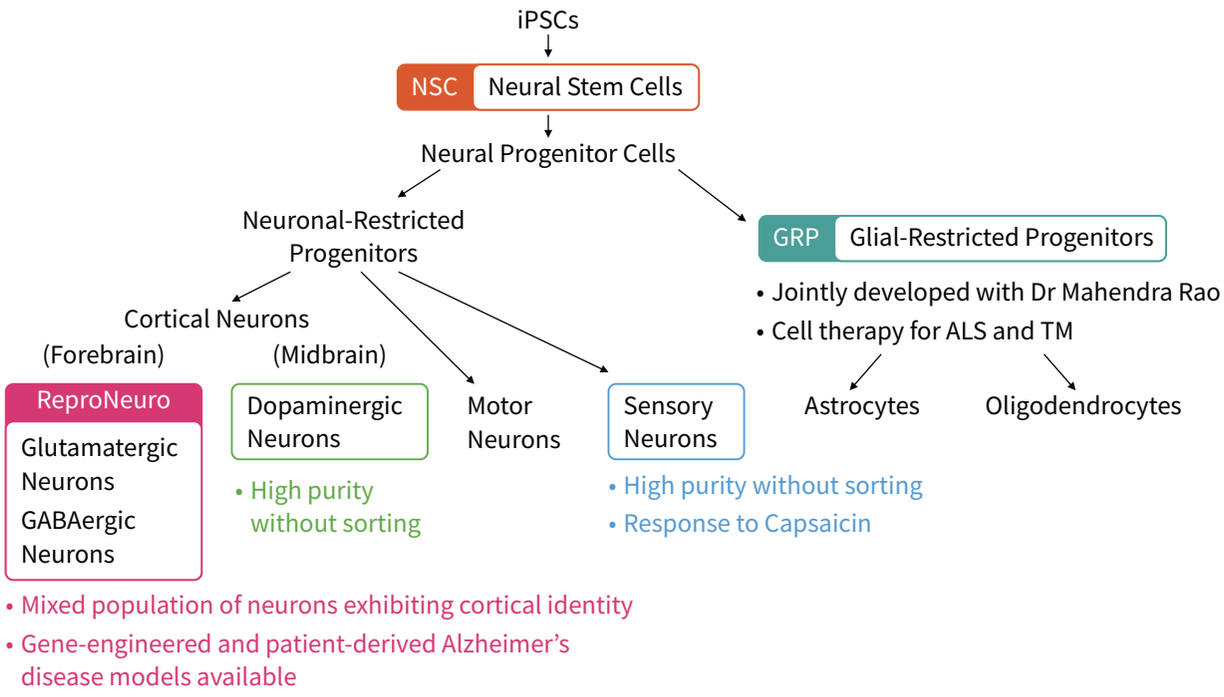


A: Immunocytochemistry. RNA-iPSCs stained with Oct4 and Nanog.
B: Flow cytometry of pluripotency genes. Nanog and Oct 4 (red). Gates are based on isoptype controls (green)
C: *In vitro* trilineage germ layer differentiation. Early endoderm (AFP in red), neuronal cells (nestin in red; β-tubulin in green) and cardiomyocytes (Troponin T in red), DAPI (blue).

The REPROCELL Tissue Network provides access to cells from donors that meet your specifications

REPROCELL can support your differentiation project to give you the type of somatic cell you need

Example: Differentiation into multiple types of neuronal cells at REPROCELL.



Contact us to begin your project: https://www.reprocell.com/research-stem-cell-services

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Neuronal Differentiation

Stem Cell Research Services

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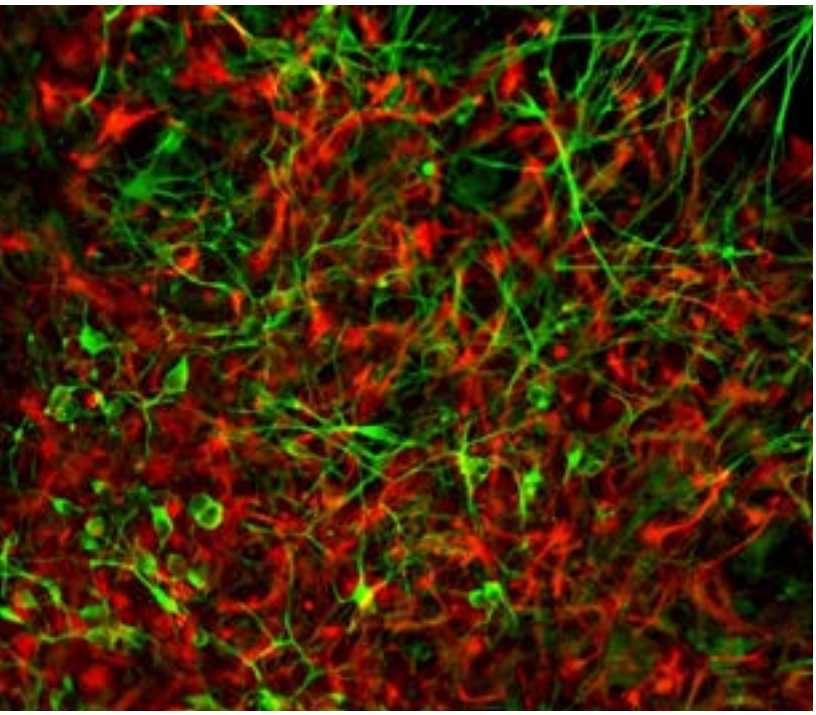

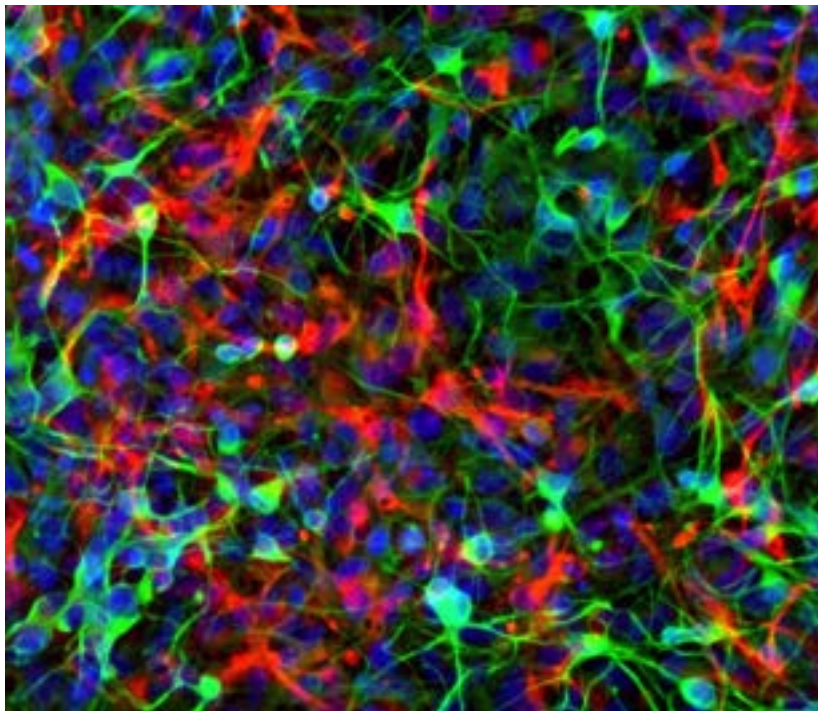

Custom Human Neurons

Looking to advance your neuro-degenerative disease research? Human iPSC-derived neurons are among the most clinically-relevant models available. Generated using tissues from your target population of choice, our iPSCs can be differentiated into human motor, sensory, or dopaminegric neurons.

For an added level of translatability, we can generate astrocytes to be cocultured alongside your differentiated cells. Our protocols provide high purity neurons (at least 70%) which can be used to model a range of nervous conditions — from multiple sclerosis to Parkinson's disease.

End-to-End iPSC Services

Many stem cell research companies specialise in neuronal differentiation. But only REPROCELL can take your model from donor tissue procurement to co-culture.

In addition to differentiation, our end-to-end stem cell services include:

- Patient screening and tissue procurement
- Target cell isolation from donor tissues
- RNA Reprogramming into iPSCs
- iPSC expansion and characterisation
- CRISPR-SNIPER genome editing

Our neurons have been used by industry leaders since 2012

REPROCELL was one of the first companies to make differentiated cell types commercially available. We launched our first commercial neurons, StemRNA Neuro (formerly named ReproNeuro), in 2012 and currently possess a wide range of iPSC differentiation capabilities. Our team have successfully delivered a diverse range of custom projects for industry, either using proprietary protocols or designing a new methodology to suit their research needs.

With over 20 stem cell scientists based across three continents, and over 15 years experience in iPSC technologies, our scientists can help you at any stage of your disease research. Overleaf, we have included some immunocytochemistry images of our differentiated neurons.

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Differentiated Neuron Subtypes

Dopaminergic Neurons

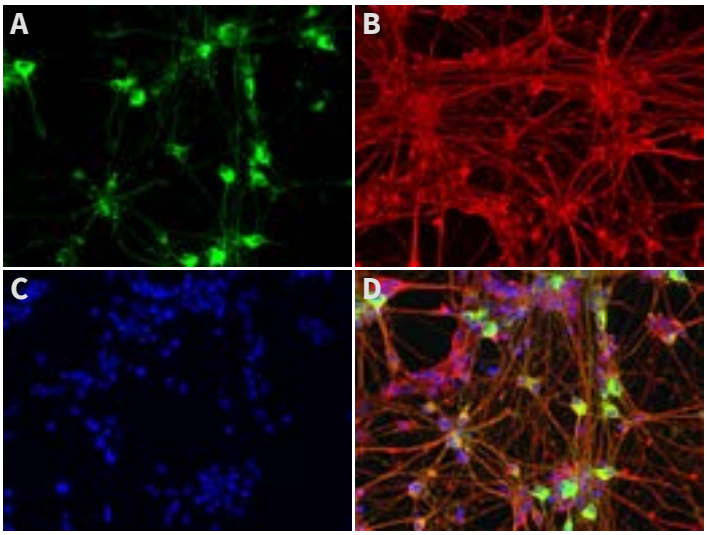

Figure 1: Parkinson's disease (PD) patient fibroblasts reprogrammed using REPROCELL's mRNA technology and differentiated to dopaminergic neurons. ***A****: TH (40-60%),* ***B****: TUJI (90%)* ***C****: DAPI* ***D****: Merge of TH, TUJ1 and DAPI*

Sensory Neurons

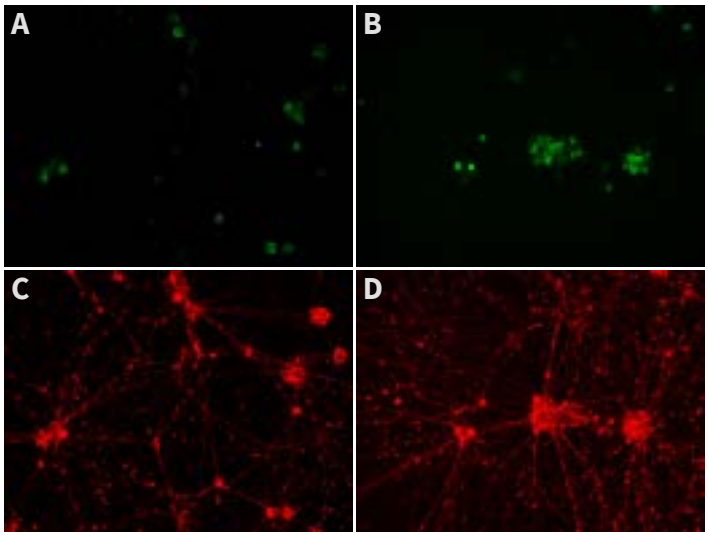

Figure 2: Our sensory neuron cultures express peripheral neuron markers and sensory neuron receptors just 4 weeks after thawing. ***A****: Nav1.8 (GFP),* ***B****: Nav1.7 (GFP),* ***C****/****D****: TUJI (Red).*

Motor Neurons

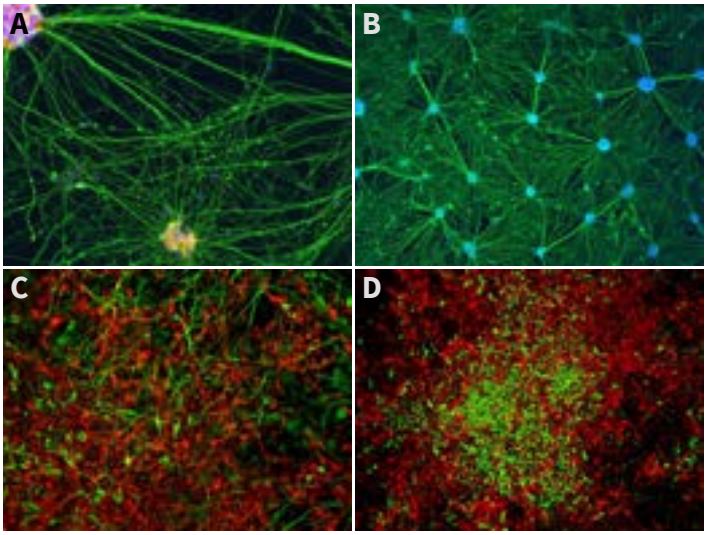

Figure 3: Our motor neurons fully mature 60 days after differentiation. ***A****/****B****: Typical expression of motor and general neuronal markers at 60 days of differentiation. TUJ1 (GFP), ChAT (red), DAPI.* ***C****/****D****: Co-culture of iPSC-derived astrocytes and iPSC-derived motor neurons. TUJ1 (GFP), GFAP (red).*

Astrocytes

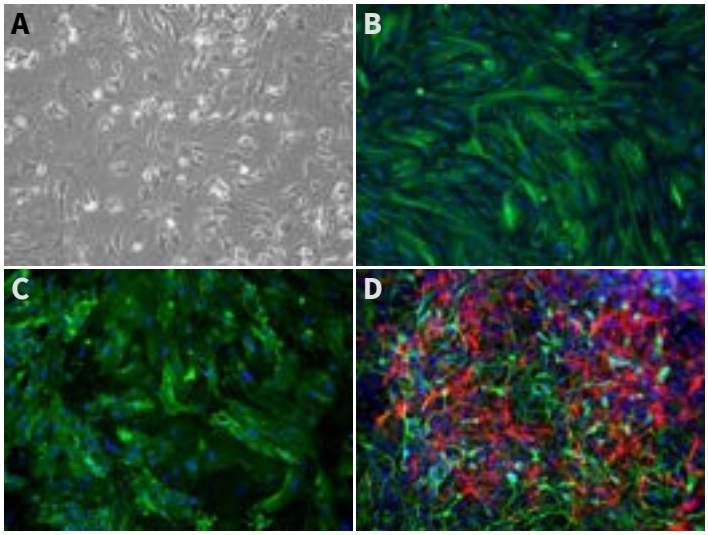

Figure 4: Our astrocytes at various stages of differentiation. ***A****: Cells exhibit large, highly cytoplasmic cell bodies just 24 days following incubation.* ***B****/****C****: Expression of astrocyte markers (****B****) GFAP and (****C****) CD44 is visible at 95 days* ***D****: Astrocytes cocultured with dopaminergic neurons. TUJI1 (GFP), GFAP (red), DAPI.*

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How we established an *in vitro* Parkinson's Disease model

In this case study, our scientists describe how they established an *in vitro* model of Parkinson's disease – from patient screening, to tissue collection, primary culture derivation, iPSC generation, and even co-culture. Read on to find out how they successfully developed this iPSC-derived assay.

Preclinical models for Parkinson's Disease

Parkinson's Disease (PD) causes progressive degeneration of dopaminergic neurons in the central nervous system (CNS). There is currently no cure for PD, and standard-of-care treatments are limited in their efficacy. New therapeutics are therefore urgently required for this genetically heterogeneous disease.

However, animal testing and 2D models often lack clinical translatability to humans. CNS tissues from real Parkinson's patients are an excellent alternative to these conventional models, as they can be derived from real, human donors affected by PD. At REPROCELL, we strongly believe that human tissue testing is the most relevant way to estimate drug efficacy prior to clinical trial. Unfortunately, fresh CNS tissues are notoriously difficult to obtain, and cannot be procured from living donors.

Alternatively, human neurons derived from induced pluripotent stem cells (iPSCs) can be generated from living patients, improving tissue access and enabling follow-up studies. These iPSCs can be transformed into a range of different neuronal cell types to create co-culture models, further increasing the clinical relevance of PD research.

How we established an *in vitro* Parkinson's disease model

We wanted to develop an *in vitro* model of PD to explore the potential applications in disease research and drug discovery. In this example, we took the model from donor recruitment, all the way through iPSC generation and functional analysis.

Here, we walk you through each step of the establishment of this *in vitro* Parkinson's disease model, including the quality control checks that we carried out at each stage. If you would like to purchase the iPSCs we used to establish this model, they are available on our website.

Step 1: Obtaining Primary Tissues

The generation of iPSCs requires tissues procured from a consenting adult patient. To ensure that our model was as clinically-relevant as possible, we wanted to obtain primary tissues from a donor living with PD.

We located a patient with a sporadic form of the disease who was appropriately consented. A skin punch biopsy was collected from the patient, transported to our labs, and then used to produce a primary fibroblast culture. Below, we have included a phase contrast image of the fibroblasts derived from this PD donor.

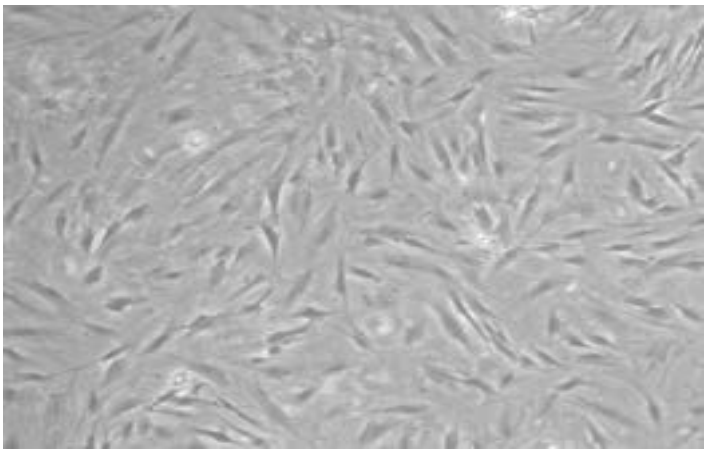

Figure 1: *Fibroblasts derived from sporadic PD patient.*

Quality control procedures we used for these primary tissues

- Immunocytochemistry (ICC) to confirm the presence of fibroblasts in the primary culture (Figure 2A).
- G-banding to confirm normal karyotyping (Figure 2B).
- Genetic profiling via STR analysis.
- Viral pathogen testing, sterility testing, and mycoplasma testing.

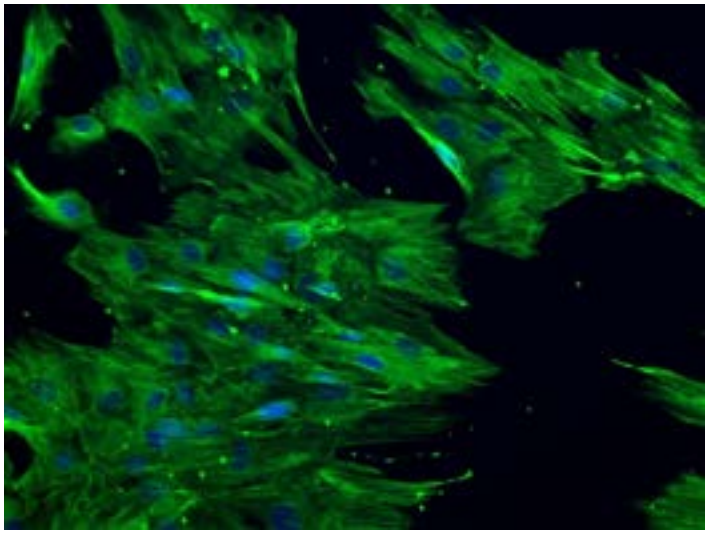

Figure 2A: *Immunocytochemistry (ICC); Vimentin (green); DAPI (blue)*

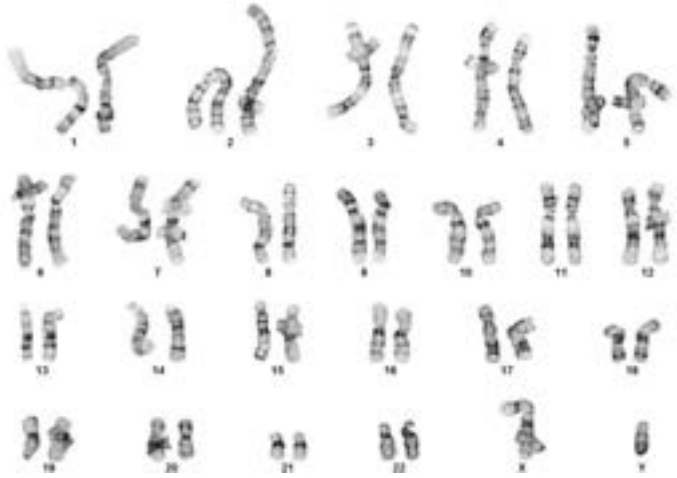

Figure 2B: *Karyotype of the donor fibroblast line*

Regulatory considerations for primary tissues

- Confirm that patients/donors have been properly consented.
- Ensure that the donor clinical data is anonymized.
- Check that the appropriate MTA is in place if primary tissues are obtained externally.

Step 2: Reprogramming primary tissue into stem cells

Following identification of a donor and isolation of the primary culture, we reprogrammed these fibroblasts into iPSCs using our StemRNA 3rd Gen Reprogramming Technology. We chose this methodology as it negates the need to screen iPSC clones, and is 50 times more efficient than other non-integrative reprogramming kits*. The StemRNA 3rd Gen Reprogramming Kit can be purchased from the REPROCELL website with a full reprogramming protocol available here.

We saw the emergence of iPSC colonies just seven days after reprogramming (Figure 3). Quality checks confirmed the potential of these cells to differentiate into any of the three germ layers. These iPSCs also exhibited stronger expression of stem cell markers than the EPCs and iPSC used in the control panel, which we purchased from ThermoFisher.

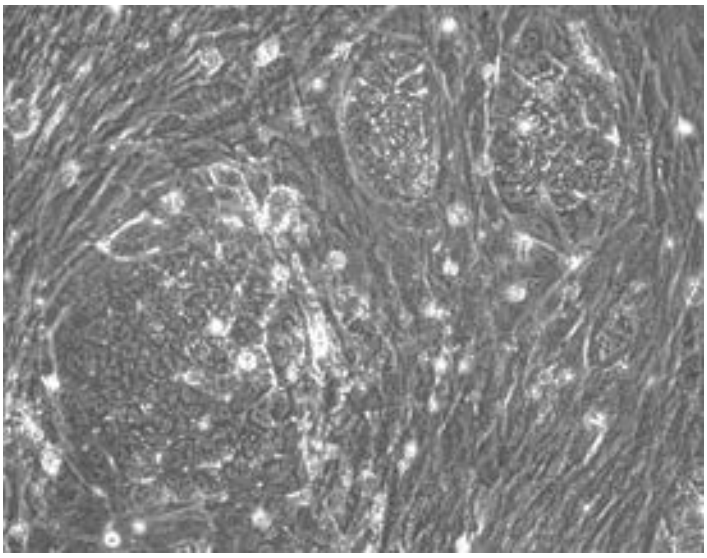

Figure 3: *Using StemRNA 3rd Gen Reprogramming Technology, we saw iPSC colonies emerging a week after reprogramming*

Quality control procedures for RNA-Reprogrammed iPSCs

- ICC of stem cell markers to verify pluripotency e.g. OCT4 (Figure 4A).
- G-banding to confirm normal karyotype (Figure 4B).
- TaqMan hPSC Scorecard Assay to demonstrate pluripotency and trilineage differentiation potential.
- Genetic profiling to check that STR analysis is consistent with the parental fibroblast line.

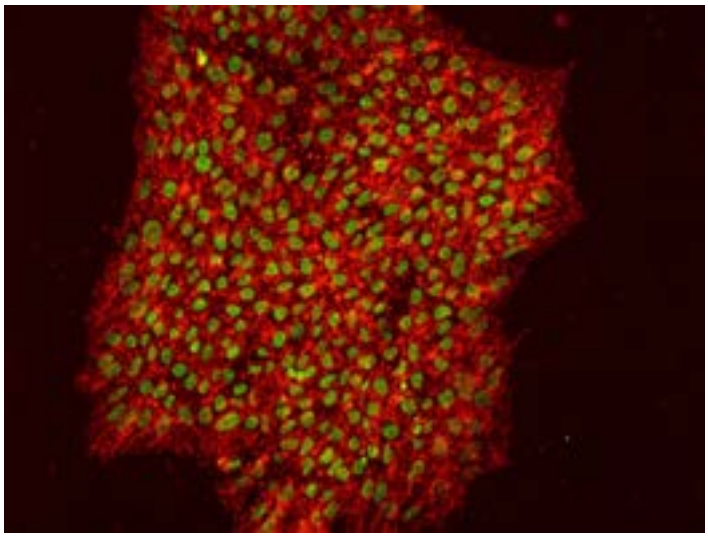

Figure 4A: *Immunocytochemistry (ICC); Oct4 (green); SSEA-4 (red)*

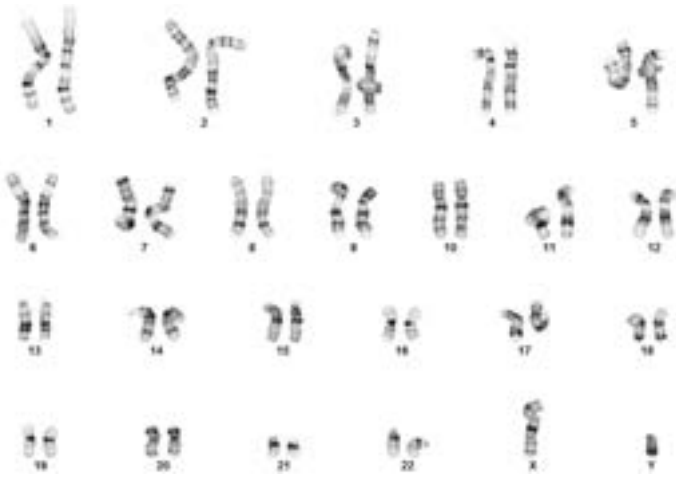

Figure 4B: *G-band Karyotyping*

Step 3: Differentiating iPSCs into Neurons

After verifying the pluripotency, karyotype, and differentiation potential of our iPSCs, we proceeded to differentiate these cells in dopaminergic neurons using a protocol adapted from Kricks et al (2011). This methodology gives rise to dopaminergic neuronal progenitor cells around day 21, and fully mature neurons before day 60.

At day 65, we had produced a homogeneous population of dopaminergic neurons that expressed the neuronal marker Tuj1, and dopaminergic markers TH/PITX3, with very few glial cells present (Figure 5A). Our dopaminergic neurons matured more quickly when cultured in MQ medium compared with astrocyte co-culture or basic differentiation media (Figure 5B).

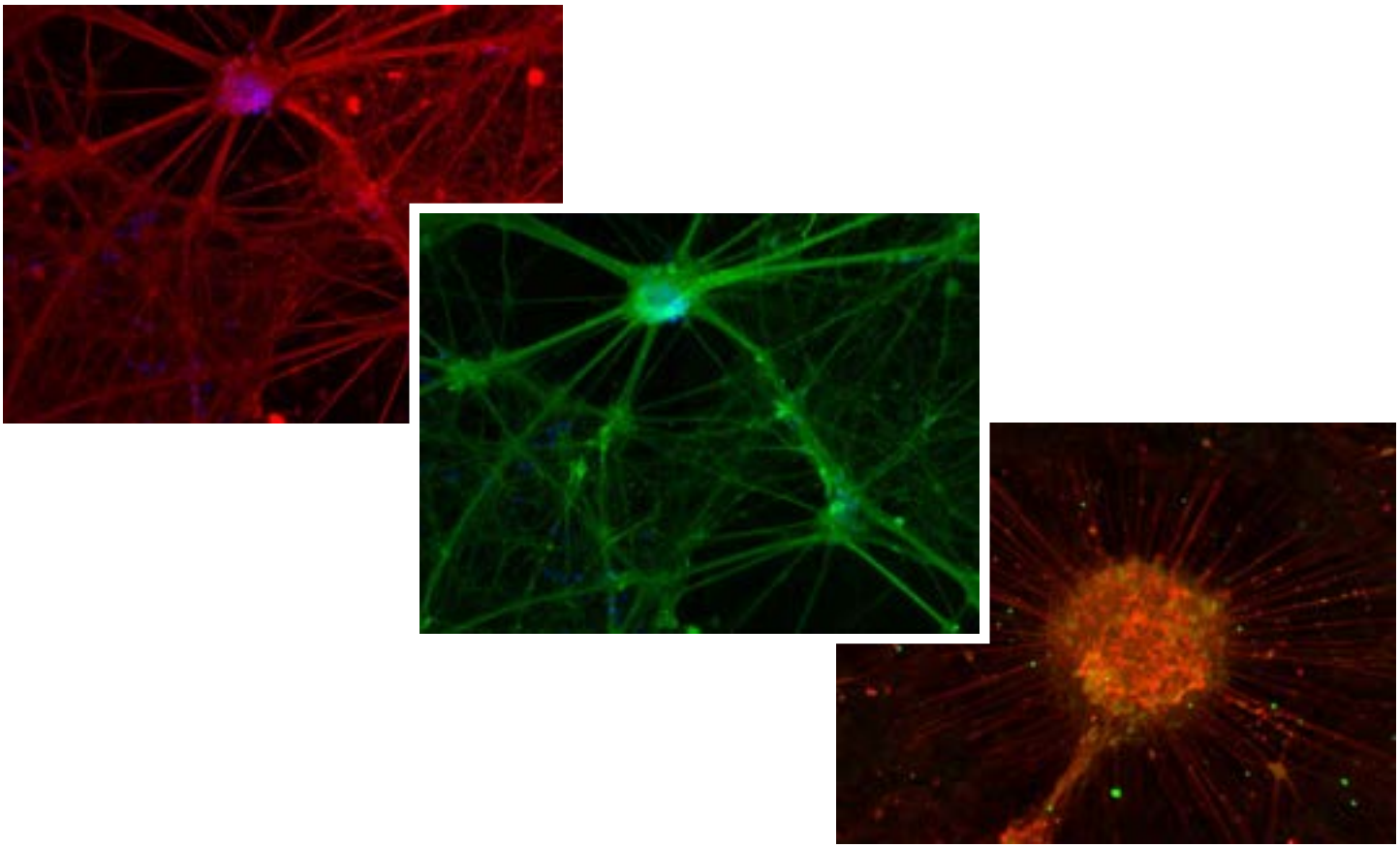

***Figure 5A: Left**: Tuj1 (red); DAPI (blue); **Center**: TH (green); DAPI (blue); **Right**: PITX3 (green); Tuj1 (red)*

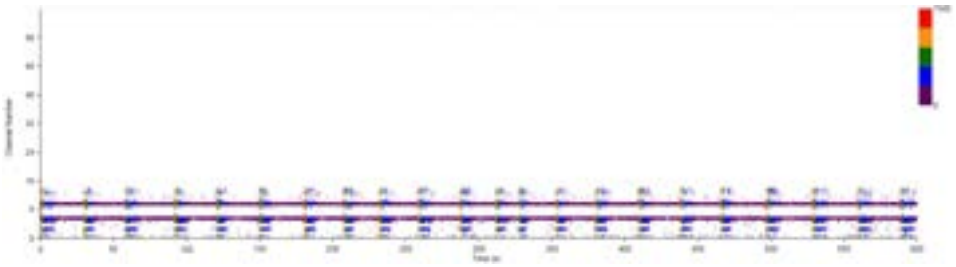

***Figure 5B:** MEA data at week 11 (Neurons 50 days old)*

Quality control procedures for dopaminergic neuron differentiation

- ICC of dopaminergic and neuronal markers e.g. Tuj1, TH, PITX3 (Figure 6A).
- MEA analysis to verify neuronal activity of mature cell networks (Figure 6B).
- RNA seq analysis to check maturity of domaminergic neurons.

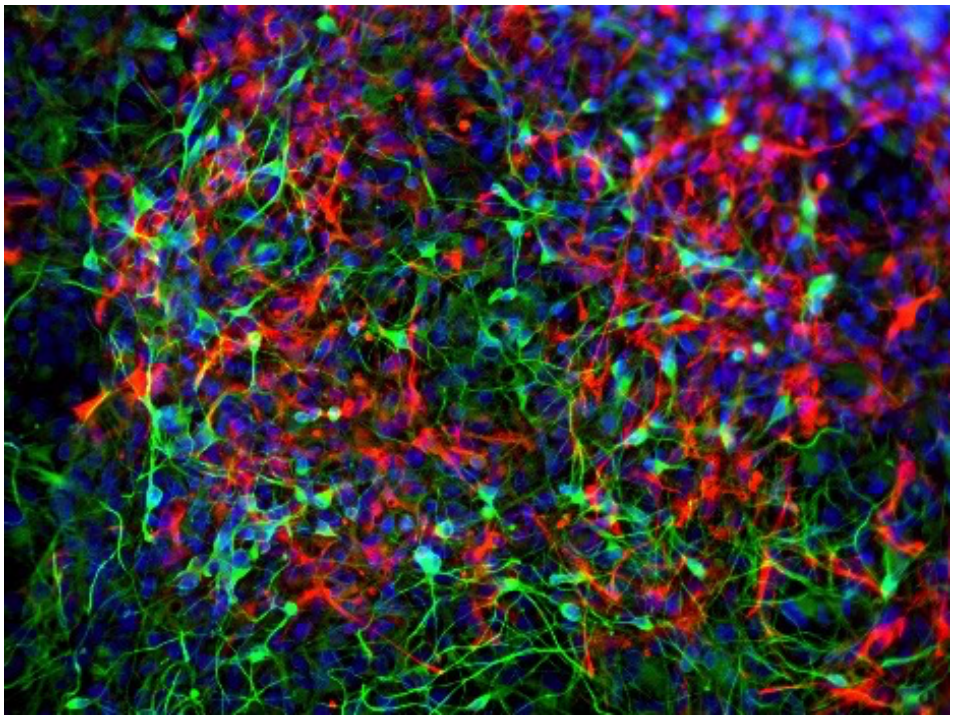

Figure 6A: *Immunocytochemistry (ICC); Tuj1 (green); GFAP (red); DAPI (blue)*

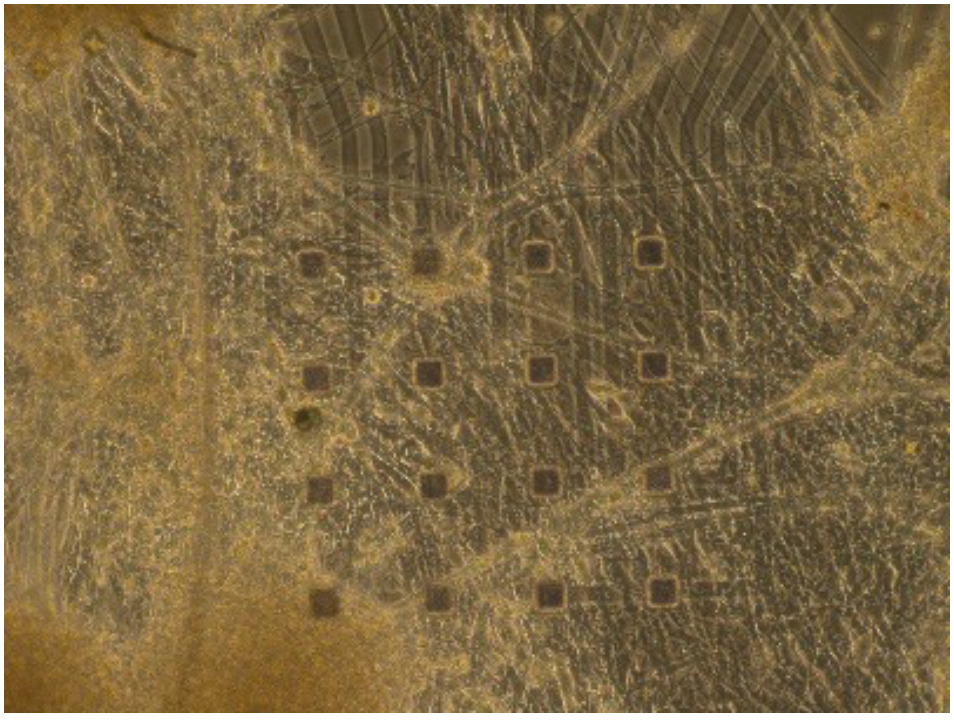

Figure 6B: *Image of mature neuronal network plus microelectrodes*

A deeper look at culture optimization and analysis

Once we had successfully derived dopaminergic neurons from our iPSC culture, we moved onto optimizing the culture conditions for neuronal maturation. It was important to show that the neurons had matured successfully, but also that they displayed functionality.

We used a range of analytical processes to ensure out culture conditions were optimal, including RNA seq and Micro-electrode array (MEA) analysis. The three culture conditions we explored for our neurons included:

1. Basic dopaminergic medium
2. MQ medium
3. Co-culture with iPSC-derived astrocytes (802-3G)

Co-culture of neurons with astrocytes

To produce the co-culture system, we had to differentiate a second control line into astrocytes. These cells were matured until day 95 where their astrocytic identity was confirmed with GFAP and CD34 staining.

However, we soon realized that a physical co-culture would not be possible for RNA seq analysis, as a pure dopaminergic neuron population would be required. We therefore cultured the astrocytes in a trans-well above the dopaminergic neurons, which allowed us to compare culture conditions without the interference of glial cells.

RNA seq analysis results

When we looked at the result of the analysis (Figure 7A), it is striking that the genetic background of the cell line is a bigger factor for differences in gene expression than the culture conditions. We found that the number of genes in common is extensive with only less than 4% being divergent (Figure 7B).

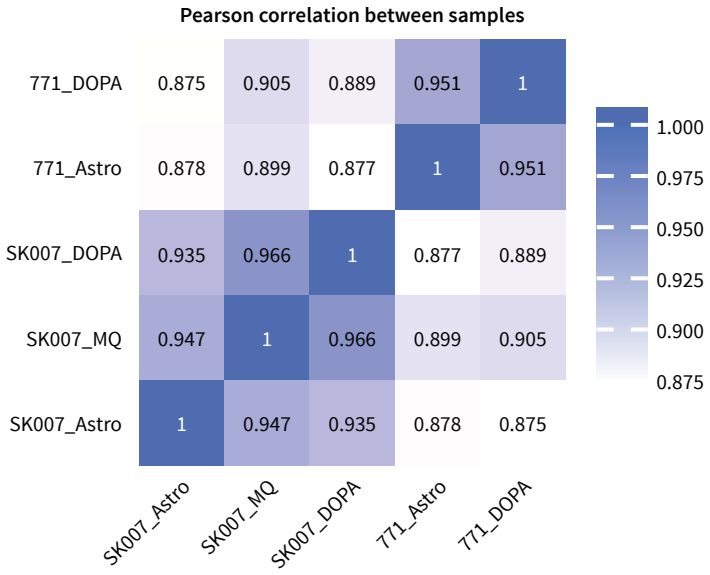

Figure 7A: *Pearson Diagram. The genetic background (control vs PD) is a bigger factor than the method of maturation (control medium vs co-culture).*

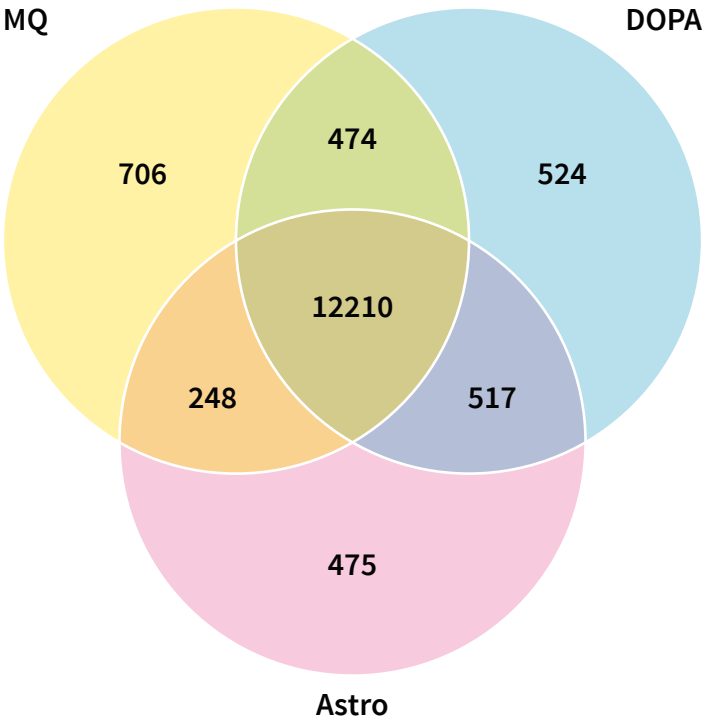

Figure 7B: *Venn diagram. The number of genes in common between culture conditions is extensive (less than 4% are divergent).*

Micro-electrode array analysis results

In preparation for MEA analysis, we plated our freshly differentiated neurons onto wells that each contained 16 electrodes. A true astrocyte/neuronal co-culture could be used for this experiment, meaning no transwells were required.

MEA recording was performed every seven days after the initial plating for a total of 12 weeks. During the first few weeks, no spontaneous neuronal firing was recorded in any of the culture conditions. After week three, we noticed an increased electrical activity in the wells containing MQ Medium and those with the co-cultured cells, but not all electrodes were firing (Figure 8A).

The results at week eleven were striking. While the co-cultured neurons displayed strong electrical activity, no synchronicities were present. Cells cultured in MQ medium displayed strong electrical activity AND the spikes were synchronous in the majority of electrodes. This is a phenomenon called bursting, which is characteristics of mature functional, neuronal networks.

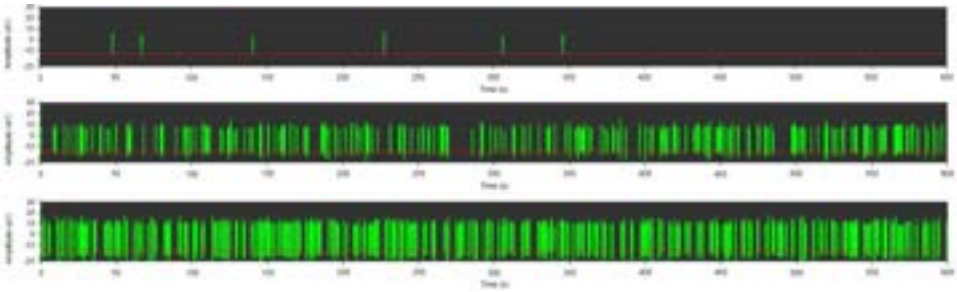

Figure 8A: *MEA data at week three (raw data). Each green line represents a spike of activity over time, and each graph represents the recording of one electrode over time.* ***Top****: Dopaminergic medium;* ***Middle****: MQ Medium;* ***Bottom****: co-culture.*

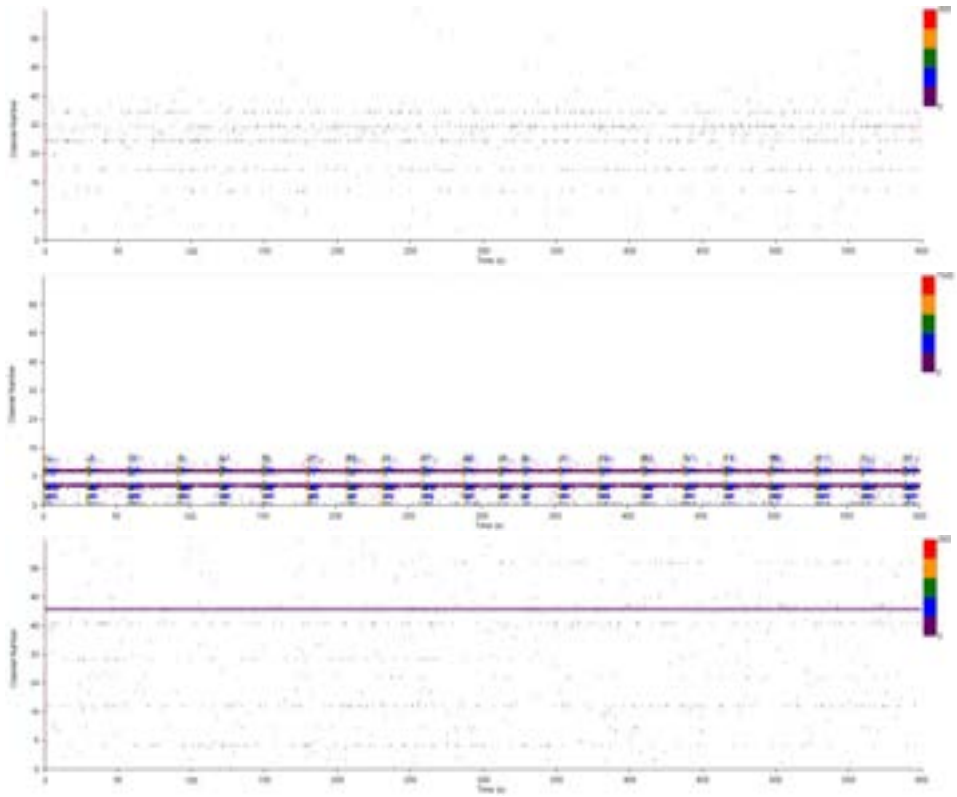

Figure 8B: *MEA data at week 11 (Rasta plots). Each group of 16 in the y axis represents the recording of one electrode, and each group of 16 in the y axis represents the recording of one well over time (x axis).* ***Top****: Dopaminergic medium;* ***Middle****: MQ Medium;* ***Bottom****: co-culture*

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Neural Differentiation Services

Lacking the time or expertise to establish your in vitro PD model in-house? At REPROCELL, we offer neuronal differentiation projects that are fully customized to your unique research needs. Decades of experience in iPSC research has allowed us to develop robust differentiation protocols for dopaminergic, motor, and sensory neurons. We are also able to offer astrocyte differentiation for clients interested in advanced co-culture systems. We can help you at any stage of your disease model journey. Inquire today, and discover how we can help make your research goals a reality.

CRISPR-SNIPER Gene Editing Service

Advanced Gene Editing for Challenging Cases

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A JOINT VENTURE

CRISPR, but better

At REPROCELL, we have collaborated with GenAhead Bio to provide CRISPR-SNIPER Gene Editing Services. This novel approach to genome modification makes it possible to achieve otherwise challenging mutations.

This makes CRISPR-SNIPER the most efficient gene-editing technique on the market. It greatly increases the likelihood of project success — saving you time, effort and money.

The Benefits of SNIPER†

- ✓ **Increase** screening specificity
- ✓ **Track** iPSC differentiation
- ✓ **Solve** challenging cases
- ✓ **Achieve** multiplex gene knock-out and knock-in
- ✓ **Save** time and money

† **S**pecification of **N**ewly **I**ntegrated **P**osition and **E**xclusion of **R**andom-integration.

	CRISPR System	CRISPR-SNIPER System
Target cells	Mainly cell lines	Cell lines and iPSCs
SNP knock-in %	< 1 %	10-30 %
Max. insertion size	~ 2 kbp	5-7 kbp
Conditions tested	~ 1	6-12
Biallelic modifications	✗	✓
KI reproducibility	Low	High

Note: The modified cells are developed, manufactured or supplied by GenAhead Bio Inc. under license from ERS Genomics Limited and Broad Institute

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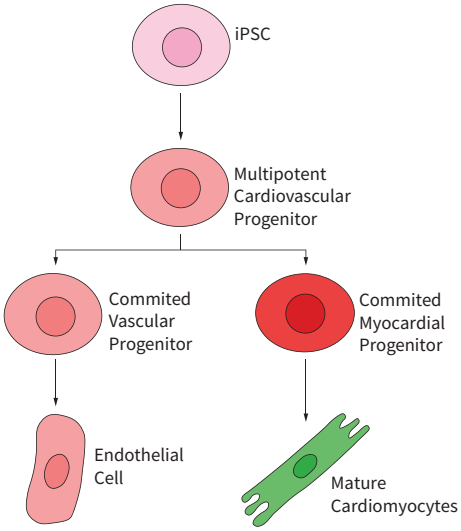
Six examples of CRISPR-SNIPER in action

1. Insertion of large gene fragments

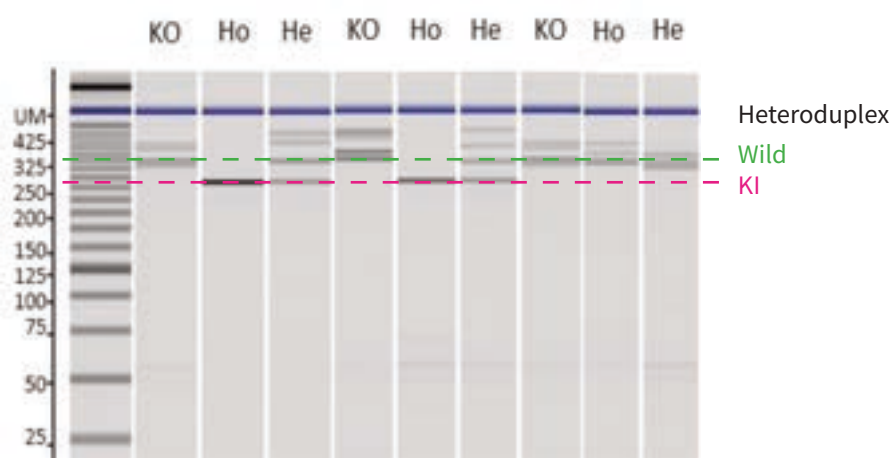
Normally, the rate of insertion decreases dramatically when your gene of interest (GOI) exceeds 2000 bp. As SNIPER allows optimization of gene editing conditions, it can be used in synergy with CRISPR to knock-in genes up to 7000 bp in size. This is particularly useful for tracking gene expression, as it makes the insertion of functional gene segments less challenging.

For example, you may want to insertfluorescent reporter genes to enable rapidoptimization of differentiation protocols or to permit tracking of specific cell populations during differentiation. Alternatively, you may want to knock-in antibacterial resistance genes to assist cell selection.



2. Insertion of Biallelic Mutations

Achieving the correct disease phenotype may require the insertion of heterogenous or homogenous mutations. However, with conventional gene editing it is challenging to achieve biallelic gene modifications. Using SNIPER, gene editing conditions can be optimized to allow the creation of heterozygous or homozygous mutants for disease modelling.



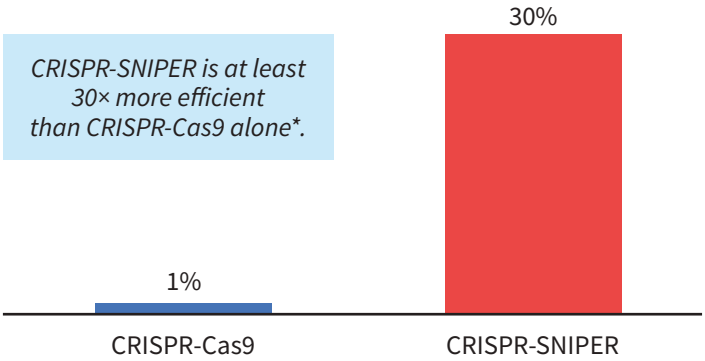
SNIPER enables editing of both DNA strands to create a homozygous (Ho) and heterozygous (He) genotype in multiple iPSC clones.

3. Increased Screening Efficiency

Thanks to SNIPER's enhanced screening efficacy, the system can detect at least 30× more positive clones than conventional screening techniques*.

In this way, SNIPER enhances CRISPR-Cas9 gene editing by making it easier to detect cells that contain your desired mutation. This means that CRISPR-Cas9 projects that were once unfeasible can be achieved.

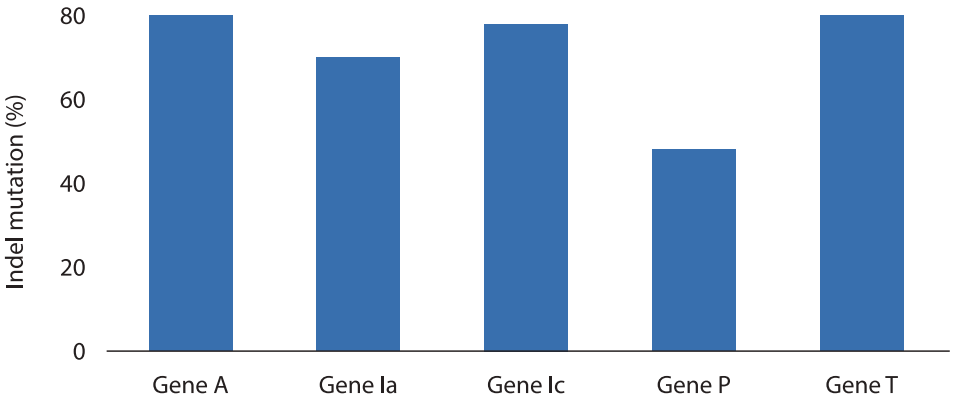
CRISPR-SNIPER is at least 30× more efficient than CRISPR-Cas9 alone.*



*For SNP modification, SNIPER screening detects positive clones at a 30× higher frequency (30%) compared with conventional screening (1%).

4. Knock-out of multiple genes without increasing cell passage number

Editing multiple genes normally involves sequential gene editing experiments, each increasing cell passage number. With the CRISPR- SNIPER system you can edit up to five genes at once, thereby avoiding the effects of extended passaging, such as slow growth, formation of genetic abnormalities, and difficulties in differentiation. A further advantage of this property is the ability to assess the effect of your modification on the interaction of numerous pathway components at once.

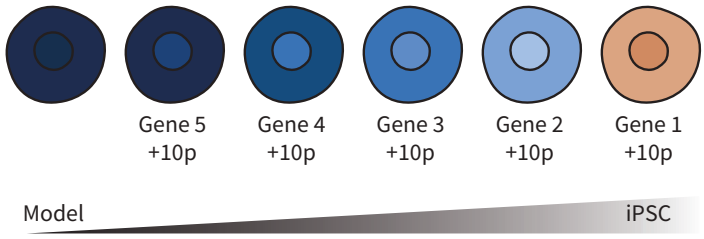


Multiplex gene KO can be achieved using a range of gRNA's with different cleavage capabilities. By optimizing the editing efficacy for each gRNA, a KO model with multiple mutations can be created After just one round of gene editing.

5. Making challenging modifications possible

Thanks to the increased accuracy of SNIPER screening, you can now fulfil gene editing projects that may be impossible using CRISPR-Cas9 alone. This is because SNIPER combines a checkerboard of culture conditions with digital PCR to pre-screen for clones most likely to possess your desired modification. By increasing screening sensitivity, CRISPR-SNIPER makes a wider range of genome modification projects possible – including SNPs, large gene insertions and function gene insertions.

With SNIPER you can edit up to five genes simultaneously.

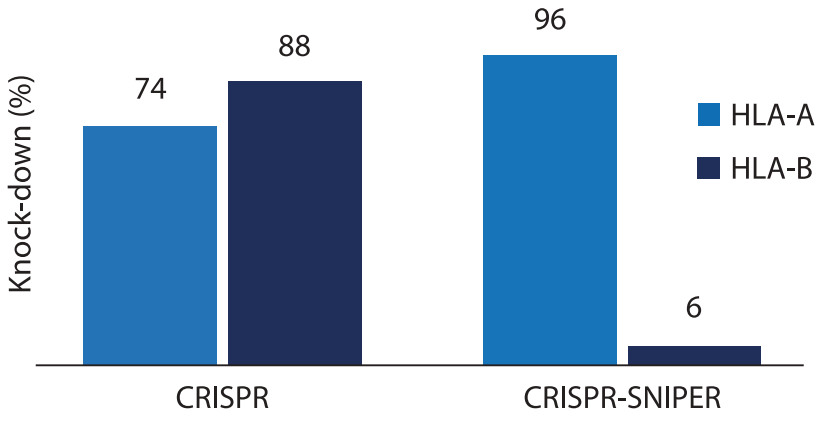


6. Achieving more accurate gene editing

It can be difficult to obtain your desired mutation if another sequence shares high homology to your GOI. By optimizing the culture conditions, guide RNA, and adding nickase to each gene editing experiment our scientists can increase the specificity of CRIPSR gene editing even further – ensuring that we only provide the cells you want.

The graph below illustrates that our optimized gRNA results in selective knock-down of HLA-A, whilst the HLA-B gene remains undisturbed. This is a large improvement over the results attained with non-specific RNA used in conventional gene editing, which results in knock-down of both alleles rather than one.

Compared with conventional gene editing techniques, SNIPER can isolate similar mutants at a high success rate.



Your Custom Gene Editing Project

Editing multiple genes normally involves sequential gene editing experiments, each increasing cell passage number. With the CRISPR- SNIPER system you can edit up to five genes at once, thereby avoiding the effects of extended passaging, such as slow growth, formation of genetic abnormalities, and difficulties in differentiation. A further advantage of this property is the ability to assess the effect of your modification on the interaction of numerous pathway components at once.

Stage 1 Bulk screening for optimal conditions

Action Points

- Optimize gRNAs
- Set Optimal Conditions
- Perform Transfection
- Complete First Screening

Check Points

- Confirm transfection condition by bulk screening with PCR

Stage 2 Scheduled cloning

Action Points

- Select Positive Clones
- Pick-up Positive Clones
- Perform Second screening

Check Points

- Verification of Gene Editing Success via PCR

Stage 3 Cell expansion and QC

Action Points

- Expansion of Positive Clones
- Quality Checks
- Cryopreservation of Cells
- Delivery of Cryovials

Check Points

- Verification of DNA sequence
- Screening Undifferentiated Marker Expression
- Mycoplasma Testing

Make REPROCELL your one-stop partner for gene editing

At REPROCELL, our scientists understand that your custom gene editing project must be as unique as your research. If you have any questions about our CRISPR-SNIPER service, please contact one of our scientists at info-emea@reprocell.com.






REPROCELL BRANDS

bioserve stemgent alvetex biopta

REPROCELL

REPROCELL provides products and services across the entire drug discovery process

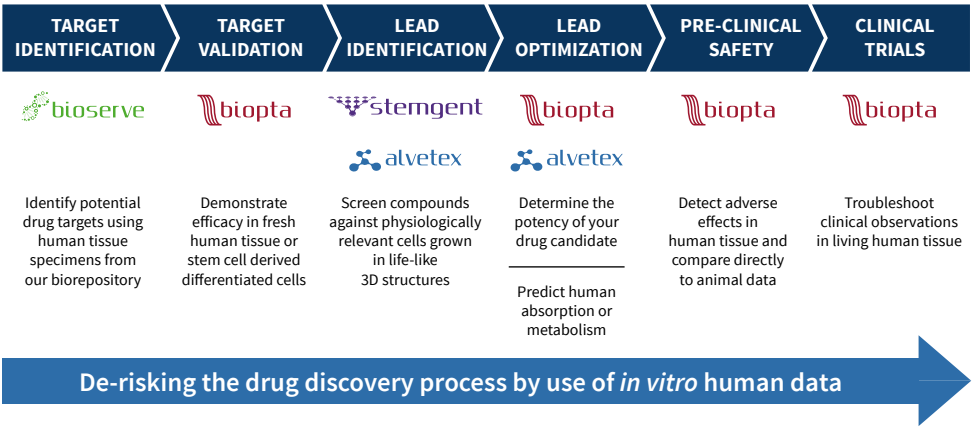
Stem Cells – 3D Models – Human Tissues – Predictive Assays

Why REPROCELL?

Clinical trials for Investigational New Drugs (IND) are perhaps the biggest cost associated with drug development. And yet, up to 90% of all INDs fail at some phase in clinical trials. This is mainly attributable to the fact that most IND research and development is done in animal models and cell culture. The translation of efficacy, clinical safety and toxicology data to humans is not assured.

The REPROCELL Group has ready access to live human tissues through our extensive clinical networks, in addition to human iPSC-derived 3D cell model systems to create custom assays that can provide predictive human data to de-risk your drug discovery programs. No other company has this unique combination of expertise and capabilities.

REPROCELL provides products and services across the entire drug discovery process



REPROCELL Brands

bioserve

- Extensive biorepository of human tissue samples
- Network of clinical sites for prospective sample collection
- Molecular services

stemgent

- RNA reprogramming systems and services
- Reagents for pluripotent cell culture and differentiation
- Extensive portfolio of small molecules

alvetex

- 3D cell culture technology creating *in vivo*-like cell environment
- Protocols for stem cell, oncology and other tissue research applications

biopta

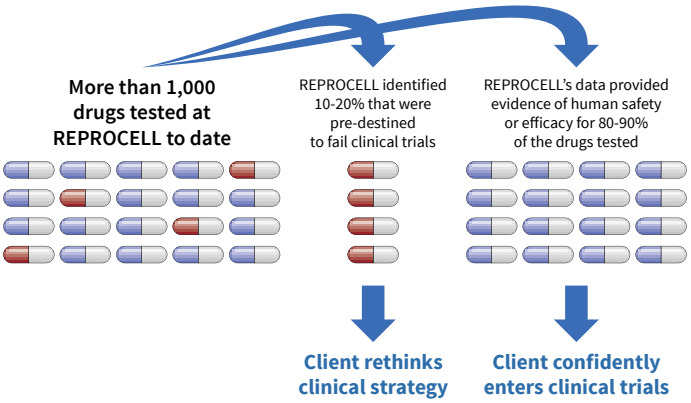
- Experts in human tissue research services for drug development
- Predictive safety, efficacy and ADME assays in human and animal tissues

REPROCELL's human tissue technology predicts clinical success by using the closest possible model of drug behavior in humans

REPROCELL offers contract laboratory services to pharmaceutical and biotechnology companies, providing data on the likely effects of drug candidates before they are given to human volunteers and patients. By understanding the safety and effectiveness of a drug in a pharmaceutical lab test, much more expensive clinical trials can be de-risked.

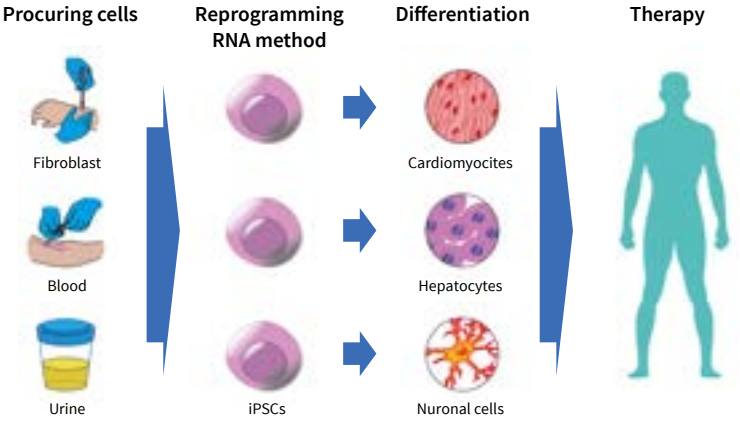
We help our clients manage risk and save money

Demonstrating human efficacy and safety at an early stage of development has an enormous commercial value to our clients' research programs. For 10-20% of the drugs we have tested, the client decided to rethink their clinical strategy which seemed likely to fail based on the human tissue data. We estimate that this has resulted in net savings of more than $55 billion in total costs for our clients.



More than **$55 billion** in wasteful costs have been avoided

REPROCELL's iPSC technology platform



1. Target Identification

Determine the biological origin of the disease and potential targets for intervention using human tissue samples. Investigate receptor sites on particular cells that may be abberantly expressed in the disease state.

The BioServe Global Human BioRepository

REPROCELL's BioServe's Global BioRepository is one of the largest commercial human tissue banks in the world.

All samples are linked to approximately 200 data points about demographic, phenotypic, pathology and diagnostic information and drug history.

We have it...

Our BioRepository contains more than 600,000 human serum, frozen tissue, DNA, RNA, FFPE and other samples collected from over 120,000 consented and anonymized patients on four continents.

Our network has it...

The BioServe Biospecimen Repository Network of partner organizations also provides broader access to rare samples and the ability to source material specific to your research needs through prospective collections.

Or, we can collect it

BioServe continues to establish procurement partnerships with speciality clinics around the USA in a number of indications/ diseases, including auto-immune, inflammatory and rheumatology, urology and oncology.

2. Target Validation

Determine the biological origin of the disease and potential targets for intervention using human tissue samples. Investigate receptor sites on particular cells that may be abberantly expressed in the disease state.

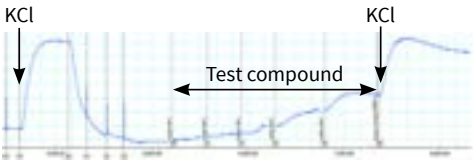
Assess the Efficacy of Your Drug Candidate in Diseased and Healthy Tissue

biopta

- Compare activation of potential target and functional response.
- Explore differences in drug response between patients and relate responses to clinical histories.

COPD lung

Healthy lung



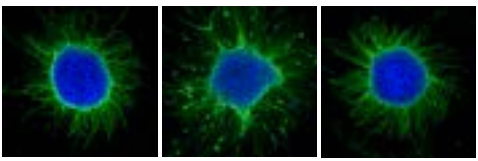
Measure bronchoconstriction or dilation

StemRNA™ Neuro —iPSC-derived Differentiated Neurons

stemgent

REPROCELL's Stemgent StemRNA Neuro* are differentiated using proprietary technologies that result in a mixed population of neuronal cell types.

- World's first commercially available iPSC-derived human neurons
- Displays highly complex networked morphology with synaptic junctions
- Alzheimer disease patient-derived and engineered mutant versions are available
- Clonally derived, highly consistent lot-to-lot performance, and stable phenotype



Neurite Outgrowth in 2D Culture. (**A.**) StemRNA Neuro, (**B.**) StemRNA Neuro AD-patient and (**C.**) StemRNA Neuro AD-mutant cells were first reformed into neurospheres and then allowed to attach to plates treated with Neuro Coat. Cells stained with DAPI (blue) and anti-TUJ-1 (green) fluorescent detection reagents.

(* Formerly known as ReproNeuro.)

3. Lead Identification

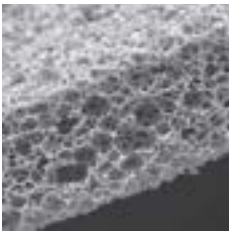
Perform high throughput screening of drug candidates on complex cell systems grown in 3D for physiologically meaningful data to identify potential leads.

Alvetex 3D Cell Culture Models

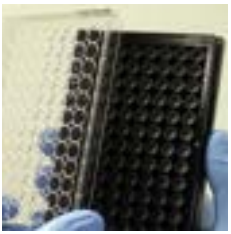
alvetex

3D cell cultures using REPROCELL's Alvetex technology deliver more *in vivo*-like results than traditional 2D monolayer cultures.

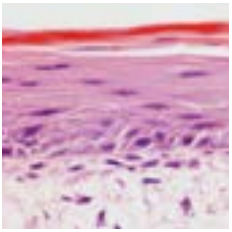
- Highly porous inert scaffold made from cross-linked polystyrene (200 µm thick).
- Suitable for a wide range of cell types including primary or iPSC-derived cells from most organs, various stem cells, cancer, and complex co-culture models.
- Automation – 96 well and 384 well plate formats compatible with high throughput screening and a variety of assays and techniques.
- Build more predictive biological models by maintaining *in vivo* physiological properties, enhancing cell viability and longevity.
- Simple histology, imaging and RNA/protein isolation analysis endpoints.
- Add perfusion in 3D for another step closer to *in vivo*.



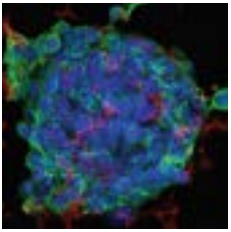
SEM of Alvetex Scaffold



96 well and 384 well plate formats available



Co-culture of primary keratinocytes and primary dermal fibroblasts forming a full-thickness human skin construct



Triple fluorescent staining of HepG2 cells grown in 3D on Alvetex Scaffold

4. Lead Optimization

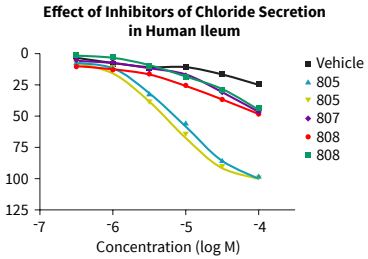
Accurately predict *in vivo* bioavailability and drug metabolism using human tissue, eliminating well known differences between human and alternative model systems.

Determine the Potency of Your Drug

biopta

- Compare the potency of your candidate drug versus other drugs on the market.

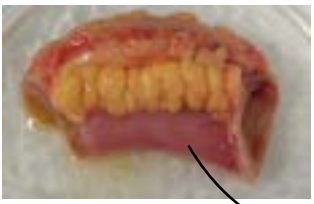
Small intestine ileum



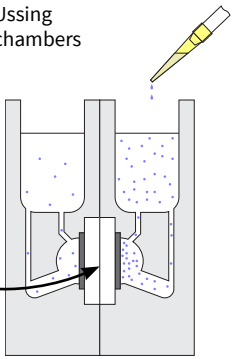
Increase the Confidence of Your First-in-Man Dose Estimate

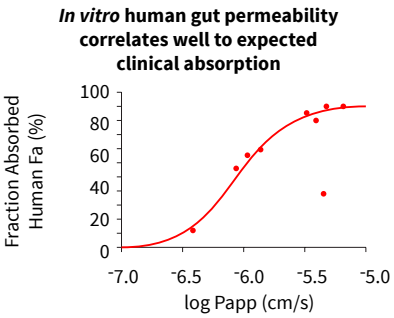
- Measure compound permeability, transporter, or metabolic enzyme activity in human intestinal tissue in order to accurately predict *in vivo* bioavailability and drug metabolism.
- Eliminate well-known differences between human and animal or cell models in bioavailability and metabolism by using human tissue.

Healthy fresh small intestine



Ussing chambers





5. Pre-Clinical Safety

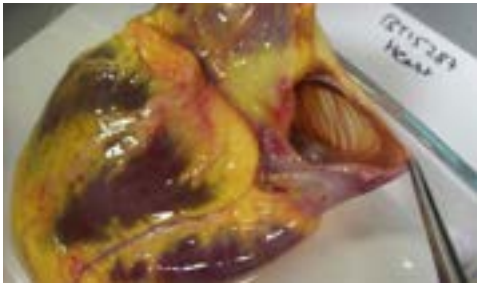
Are your test compounds safe in humans? Evaluate the pre-clinical safety of compounds using human tissue.

Find Out if Your Drug is Safe in Human Tissue Prior to Clinical Trials

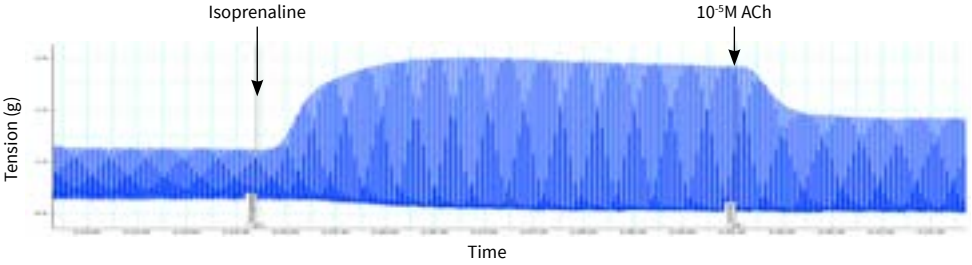
biopta

- Measure adverse effects on heart or lung muscle contractility or blood vessel contraction/ dilation.
- Conduct comparative studies across species.

Human heart



Force of contraction measured in organ baths



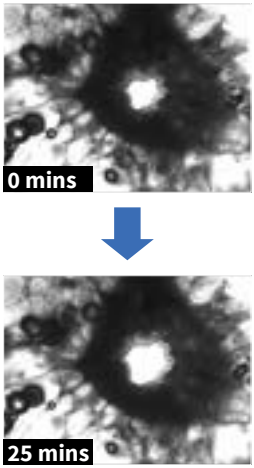
6. Clinical Trials

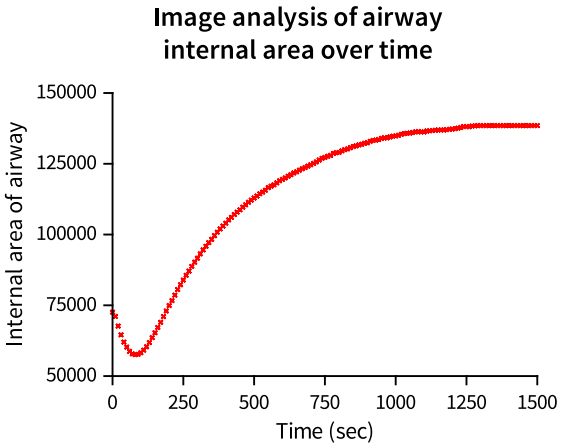
Troubleshoot clinical problems by investigating the mechanisms of clinically-observed adverse effects using human fresh tissues.

Investigate Unexpected Side Effects Observed in Clinical Trials

biopta

- Obtain independent verification of your clinical results.
- Examine adverse effects e.g. unforeseen effects on bronchiole dilation effecting airway internal area over time.



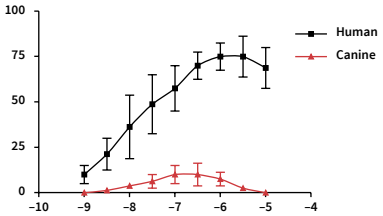


REPROCELL generates high quality translational data to help you make informed decisions during drug development.

Only a selection of our available tissues and assays is shown.
See our website or contact us for more information.

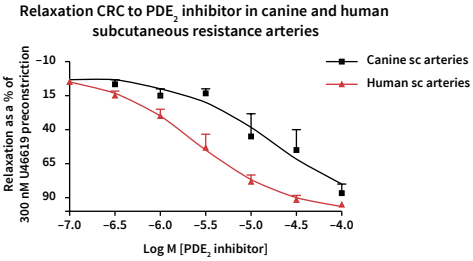
REPROCELL can directly compare drug responses across species, helping you to translate your data from preclinical animal species to humans

It is generally recognised that there is an over-reliance on animal models in the prediction of clinical effects, in particular with respect to the demonstration of efficacy in humans and the translation from preclinical species. Biopta's ability to perform comparative *in vitro* studies, including human tissue, highlights potential species differences early in the drug development process. This has become especially important in translational medicine, through preclinical safety studies and the need improve the prediction of efficacy by using phenotypically-relevant fresh diseased human tissue.



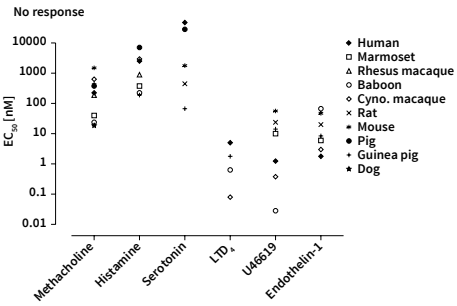
For example, the 5-hydroxytryptamine (5-HT, serotonin) pathway is more prominent in the coronary artery function of human than in canine tissues, a standard preclinical safety species and pig, a favoured cardiac model species. The above graph shows the marked differences in responses of isolated arteries to 5-HT between humans and dogs.

A further example below shows clear differences in the potency of a PDE type 2 inhibitor in humans and dogs, such that assessment of test compound effects in dogs would under-estimate the effect in humans.



It is not only in the vascular system that such differences exist between species.

A review of the literature illustrates that the potencies of various bronchoconstrictors differ markedly between the main preclinical species (see comparison below), with no species mimicking the human situation. Approximately one-third of all respiratory abnormalities during human clinical trials can be attributed to unforeseen drug-mediated changes in airway resistance. Taken together, these findings suggest that the prediction of human bronchoconstriction (and therefore airway resistance) could be vastly improved by greater use of human fresh bronchial tissues or by an early cross-species comparison between preclinical species to explore the relevance of the animal model to humans.



Adapted from:
Seehase *et al.* (2011) *J. Appl. Physiol.* 111:791-798
Downes *et al.* (1986) *J. Pharmacol. Exp. Ther.* 237:214-219

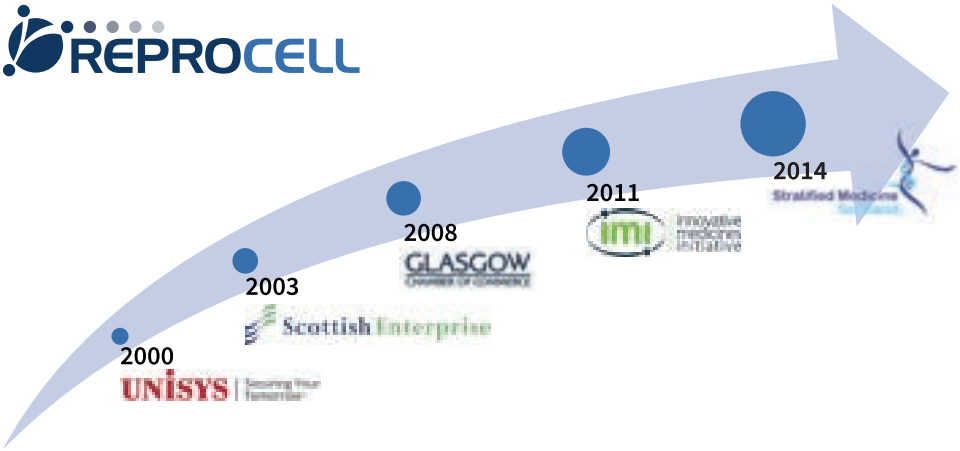
Although animal models continue to be a mainstay in the testing of potential new drug therapies, early cross-species comparisons with fresh functional human tissues increases confidence that the results will translate to patients. Moreover, such assays play an important role in the "3Rs", the refinement, reduction and replacement of tests in animals.

REPROCELL (formerly Biopta) has been providing contract research services to the pharmaceutical industry since 2002 and has established itself as the world leader in the use of fresh isolated tissues to better predict drug activity prior to clinical trials. The clear commercial benefits of reducing risk by generating early human data on safety, efficacy and absorption are making human tissue research a routine part of drug development. REPROCELL's expertise in all areas of human tissues research including sourcing, handling and experimenting on human tissue allows us to act as your "Human Tissue Research Department".

To discuss a comparative *in vitro* pharmacology study across species at REPROCELL please contact **info-emea@reprocell.com**

Award Winning Business

At REPROCELL, we have been awarded several titles for our work in human tissue research, including the Scottish Enterprise SMART Award (2003) and the Innovative Medicines Award (2012). Today, we are the preferred vendor of the Medicines Discovery Catapult (2019) and remain world-leaders in human tissue research globally.



Fulfilling Your Research Goals

REPROCELL work with a variety of clients, ranging from the top 20 Pharma to virtual biotechs. Numerous companies have also published using data generated in REPROCELL's labs. Below you can find a collection our client testimonials and publications.

Testimonials

"*[REPROCELL] has provided Proteon with high quality data in human tissue to guide dose selection for human clinical trials. The information has and will continue to be an important part of our nonclinical data for regulatory submissions.*" — **Senior Vice President and Chief Medical Officer, Proteon Therapeutics Inc.**

"*[REPROCELL's] human tissue services have played a critical part in our compound selection and have added considerable value to our lead compound. At our last round of funding, the investors were reassured by the presence of functional data on living human tissues.*" — **President & Head of R&D, Canadian Biotech.**

Publications

Lynch *et al*. **Comparison of the Intrinsic Vasorelaxant and Inotropic Effects of the Antiarrhythmic Agents Vernakalant and Flecainide in Human Isolated Vascular and Cardiac Tissues.** *Journal of Cardiovascular Pharmacology* 61:3 226–232 (2013).

Skinner *et al*. **The contribution of VEGF signalling to fostamatinib-induced blood pressure elevation.** *British Journal of Pharmacology* 171:9 2308-20 (2014).

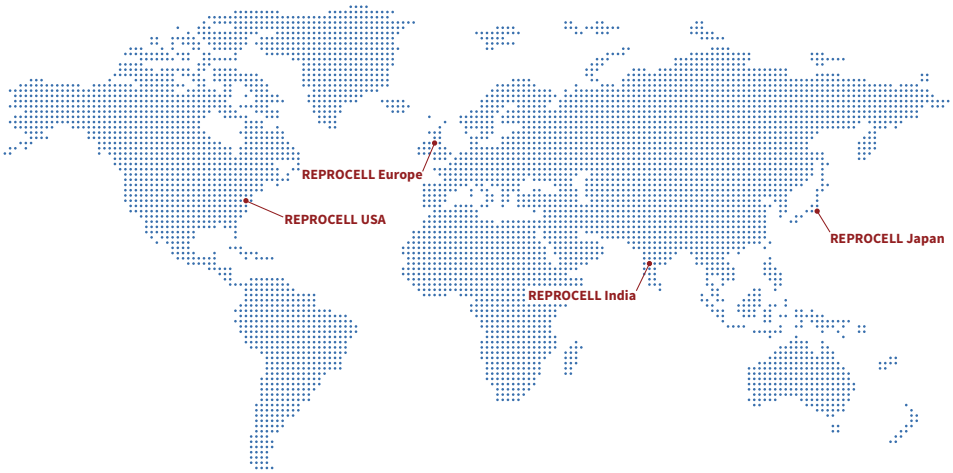
Figure 1: Whole human organs and tissues can be obtained from our global network of biorepositories.

Figure 2: Patient derived cell lines can be obtained for iPSC transformation and differentiation.

Figure 3: Our scientists can then use these tissues to test the safety and pharmaco-kinetics of your test agent.

Figure 4: We can also measure test agent efficacy and investigate the cause of adverse drug reactions.

REPROCELL worldwide



NEVER SAY NEVER
ロート製薬

Development and contract manufacturing of products related to regenerative medicine

What is CMO/CDMO?

CMO (Contract Manufacturing Organization) and CDMO (Contract Development and Manufacturing Organization) refer to outsourced contract services related to drug manufacturing (investigational and commercial drugs)

ROHTO offers CMO/CDMO contract services for regenerative medicine and other related products based on know-hows and technologies we have cultivated over the years


Clinical Trials

NEVER SAY NEVER
ロート製薬


Cell Processing

Mesenchymal Stem Cells

CMO/CDMO


Medium Development


Development of Automated Culture System

Strong in Commercialization

Developing cell therapies in-house and have know-hows needed for commercialization.

Can also offer support for pharmaceutical application in Japan.

Can Use AOF※ Medium

Providing stem cells using culture methods that do not rely on animal- or human-derived components.
※AOF=Animal Origin Free

Optimization of Culture Methods

Constantly developing culture methods that are suitable for stem cells and can propose optimal culture conditions for them.

Development and commercialization process of products related to regenerative medicine

Ex)

CMO/CDMO service

- Creating Standard Operating Procedure
- Manufacturing sample materials for clinical research
- Performing quality testing and characterization
- Manufacturing sample materials for pre-clinical research
- Process Development and Process Optimization Study
- Creating Standard Operating Procedure
- Manufacturing and storing of cells used for therapy
- Performing quality testing and characterization
- Manufacturing and storing of cells for launch
- Performing quality testing

Features of ROHTO's CMO/CDMO Services

01 Cell Culture Technology

- In-house GMP/GCTP
- Manufacturing and development
- Scale-up study (ex. Cell culture using floating methods and multi-layer flasks)

02 Quality Control Testing (including outsourced test)

- Asepsis test
- Endotoxin test
- Mycoplasma detection test

AOF
Animal Origin Free

03 Contract Manufacturing of Culture Medium

- Formulation development (improvement of proliferation, development of serum-free culture media)
- Manufacturing and development (scale-up study)
- Contract manufacturing (in-house GMP)

NEVER SAY NEVER
ロート製薬

Flowchart of outsourcing

Contact by e-mail → Meeting with sales team → Signing of nondisclosure agreement → Meeting with person in charge → Quote → Contract Conclusion

■ Contact us:
ROHTO Pharmaceuticals Co., LTD.
6-5-4 Kunimidai, Kizugawa, Kyoto 619-0216, Japan Rohto Research Village Kyoto
E-mail: rm-cdmo_info@rohto.co.jp

Rohto Regenerative Medicine search

https://www.rohto.co.jp/company/business/cdmo/cmo-cdmo/

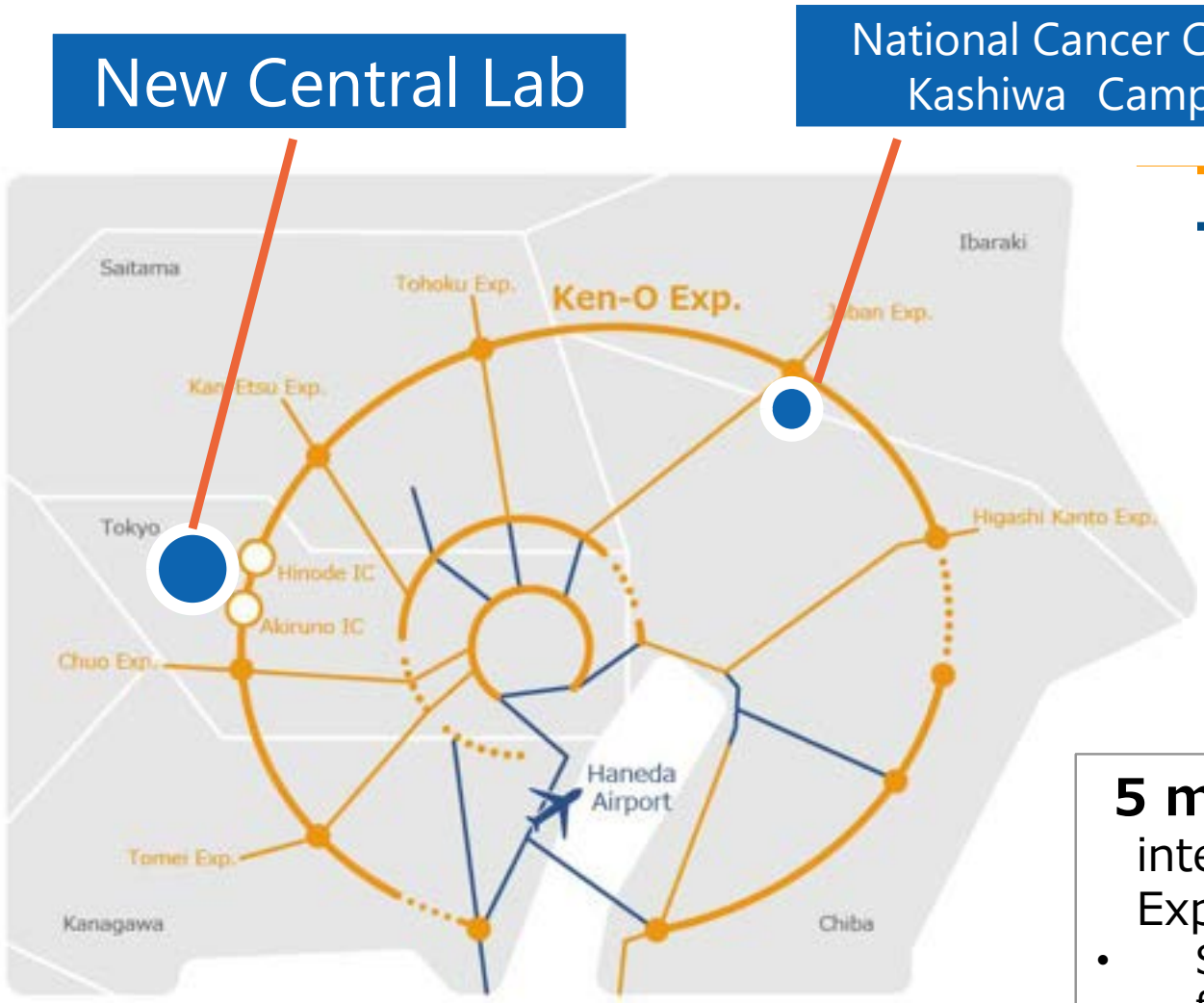
2022.6.22 / 1,000

SRL ～ H.U. Bioness Complex ～

SRL ; New Central Lab in Akiruno City, Tokyo Prefecture

- ✓ The largest testing capacity in Japan
- ✓ Fully-automated laboratory for general diagnostic tests
- ✓ R&D facilities to lead to the creation of new businesses in the future

Access



5 minutes from the Hinode interchange (Ken-Oh Expressway)

- Smooth access for general tests from the Kanto area
- Esoteric tests will come from across Japan by air (Haneda Airport) and via the expressway

H.U. Bioness Complex（Outline）

TECH

T-Cube [Laboratory building]

Laboratories with the latest testing technology

INNOVATION

I-Cube [R&D building]

An R&D center for advancing knowledge and innovation

SOCIAL

S-Cube [Administration building]

A gateway that connects us with society

WELLNESS

W-Cube [Welfare building]

Welfare functions that promote health and wellbeing

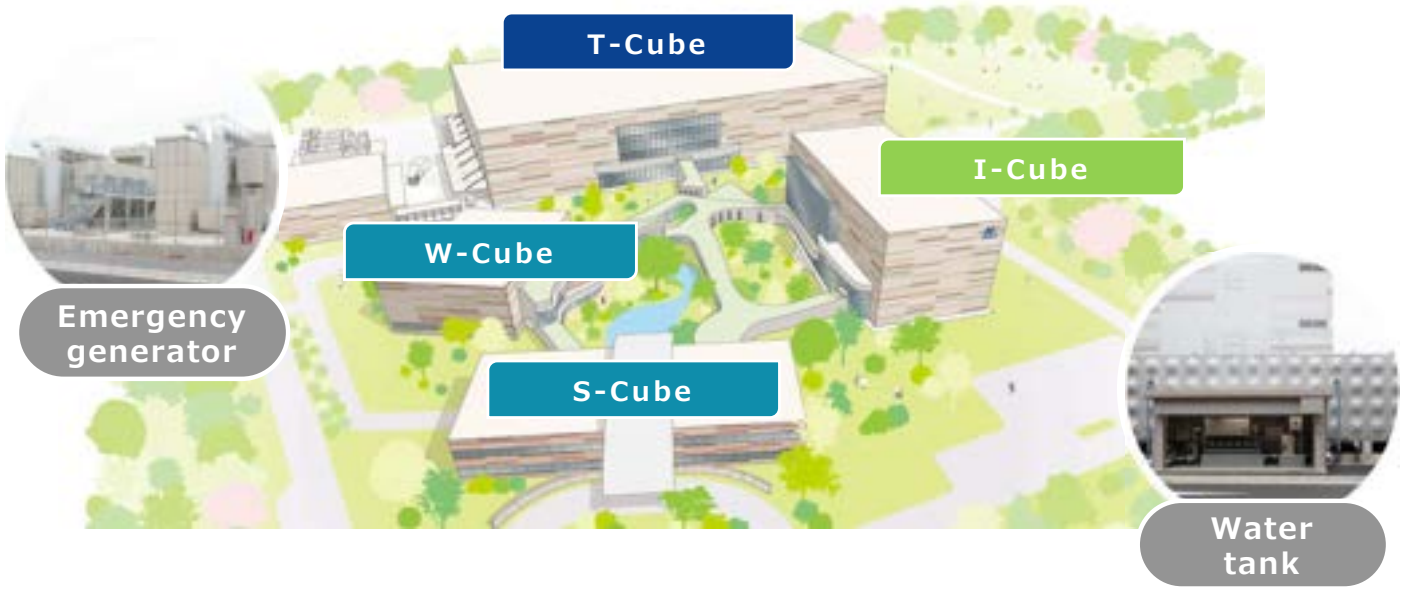
Charge Dining / Cafe

H.U. Forest Hall

H.U. Bioness Complex（Facility overview）

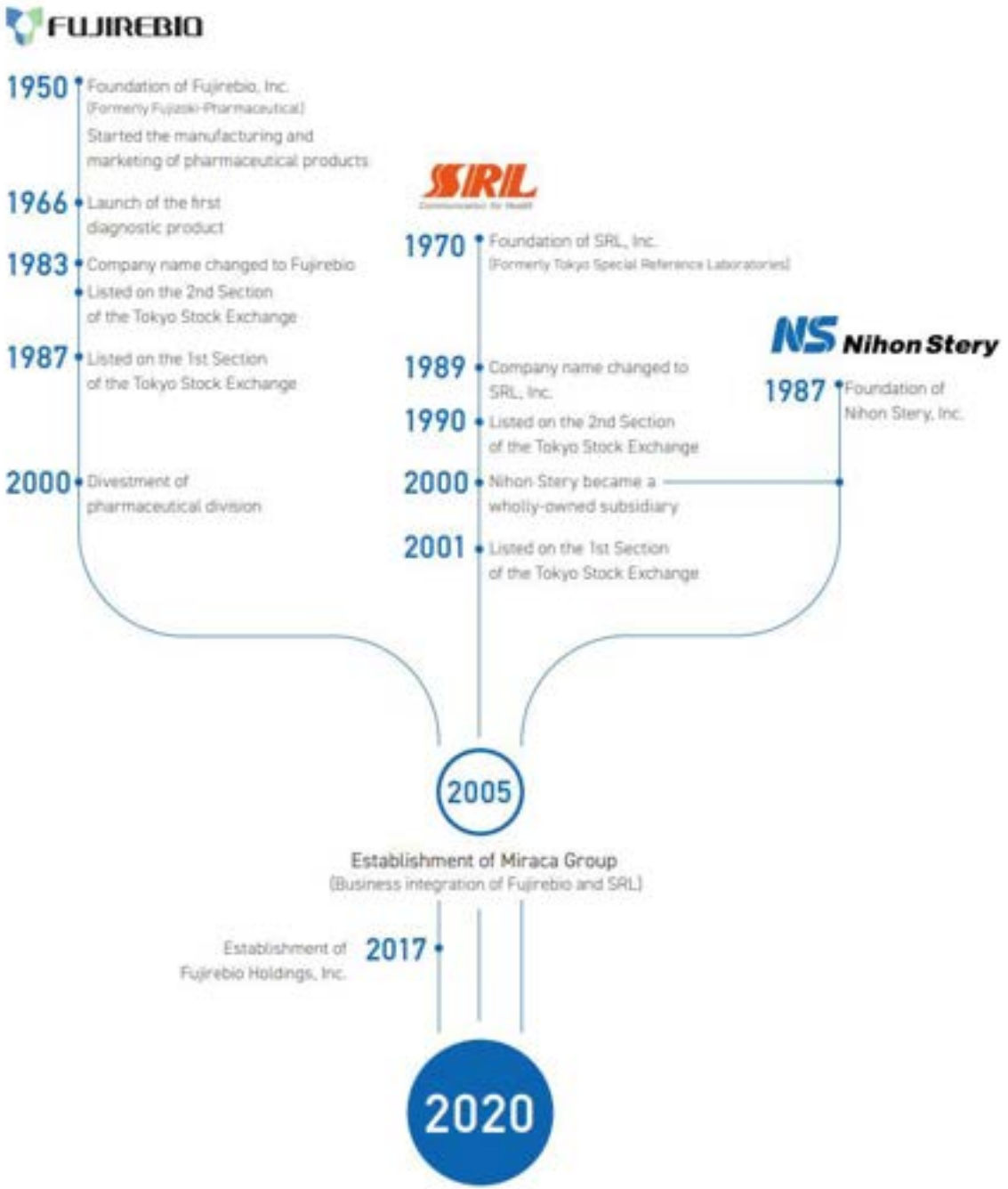
Non-stop testing service even during disasters

- ✓ Seismic isolation structure and earthquake-resistant construction
- ✓ Infrastructure functions (emergency water tanks and emergency power generators) are secured to enable to continue testing for 3 days (72 hours) in the event of a disaster



	T-Cube	I-Cube	S-Cube and W-Cube
Floors	・1F : Reception,General automated testing ・2F,3F : Special testing	H.U.Group Research Institute and Fujirebio Development devision	Admin building : Reception, meeting room, international conference hall Welfare building : Multipurpose hall, training room, cafeteria
Floor space	About 46,000㎡	About 10,000㎡	About 10,000㎡
Structure	Seismic isolation	Seismic isolation	Seismic

History of H.U. Group



Areas of Business / Annual Sales

Areas of business

Consolidated net sales

FY 2020
223.0 billion yen

FY 2021
272.9 billion yen

FY 2022
260.9 billion yen

Employees / Group Companies

Employees

Number of permanent employees

5,444

Number of temporary employees:

6,495

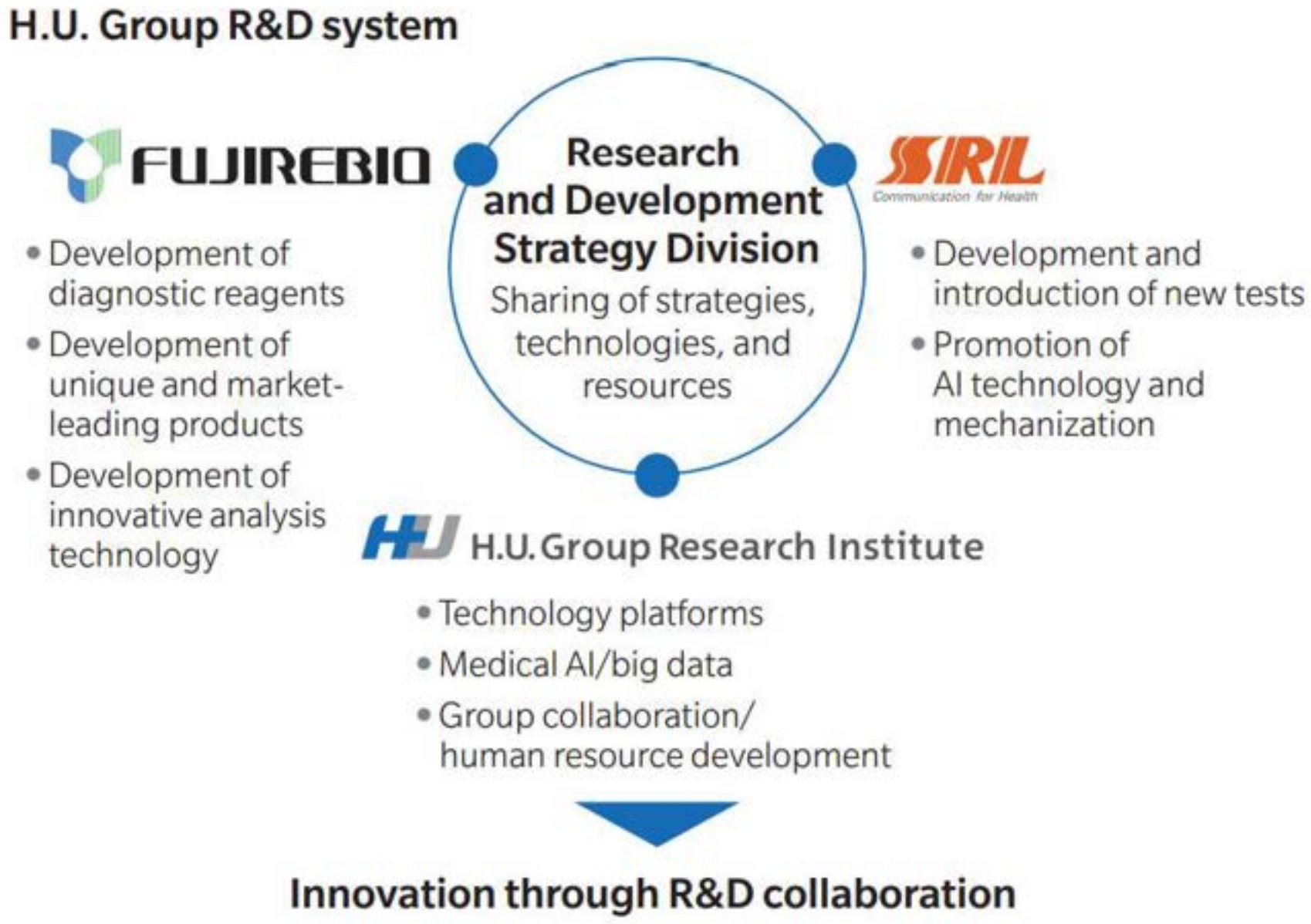
As of March 2022

Group Companies

See here for details →

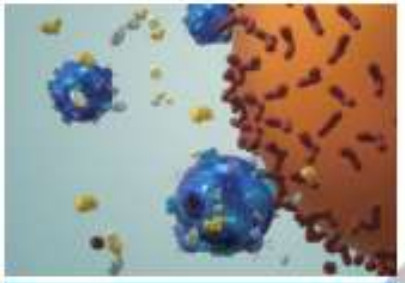
As of March 2022

H.U. Group R&D System



Promoting technology development for next-generation medical treatment and healthcare

Unique and world-leading R&D based on diverse and highly qualified human resources



Wet laboratory
Immunochemistry / Biochemistry / Genetic engineering

Dry laboratory
AI / Programming / Data science

Basic research in new fields

Next-generation analysis platforms

Medical big data / Medical AI

Genomics/omics analysis platforms

Manufacturing
Various processing operations / Molding / Development of systems and apps

Increasingly Sophisticated Medical Care: Genomic/Omics Analysis

SRL

AkirunoCube T-cube

Pathology	Nucleic acid extraction/Genes	NGS/Genome
• Preparation of slides by embedding, sectioning and staining tissue samples • Digital pathology	• Extraction of nucleic acid from embedded tissue and personalized genetic testing • Quality evaluation • Extraction methods to meet various needs	• WGS/WES • RNA-Seq etc.

Integration of technology platforms required for personalized medicine of the future within the same laboratory/area

+

R&D

LTS

Corporate

IVD

Early implementation of new technologies and platforms both inside and outside the company

H.U. Bioness Complex
AkirunoCube

Contract Quality Testing Service

Biopharmaceuticals / Genetic therapy / Regenerative medicine

We support to the development of healthcare through regenerative and cell medicine and gene therapy.

Quality Testing Features

Microorganism / Virus

We offer a variety of tests.

SRL Communication for Health

SRL conducts each of tests, a member company of H.U. Group.

GMP/GCTP

We perform the request and audit from GMP/ GCTP facilities

1 Contract Quality Testing Services

We performs testing required by regulations for biopharmaceuticals (biotechnology-applied drugs/biologically derived drugs).

- Sterility test
- Bacterial Endotoxins Test
- Mycoplasma Testing etc.

2 Chromosome karyotype test

We offer our advanced chromosome analysis technology.

- G-band
- SKY
- FISH

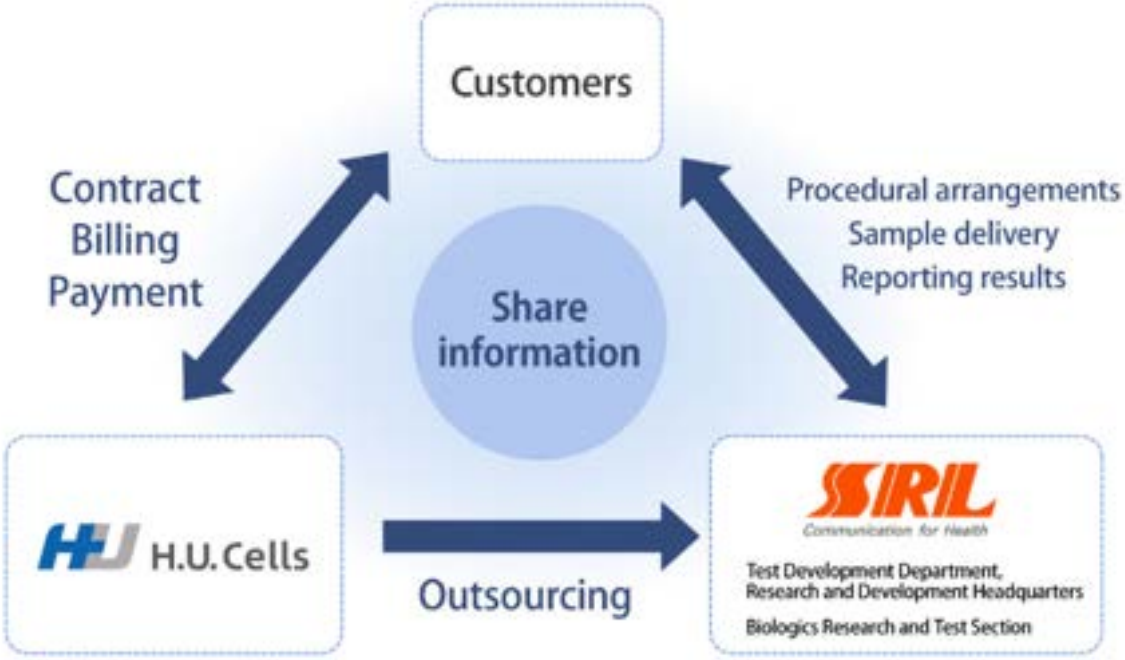
3 Laboratory test Quality test

- We perform virus testing, etc. for donors who donate human cell material.
- We perform virus testing, etc. for donors who donate human cell material.

4 Contract CPC Manufacturing Services

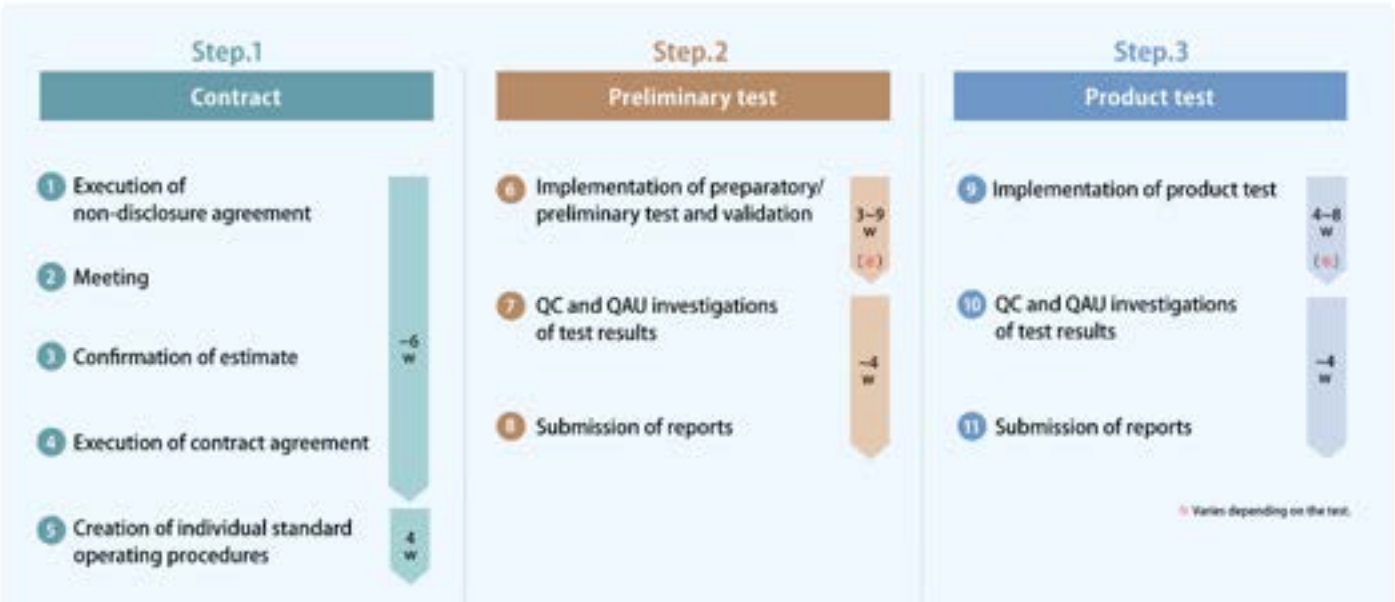
- Please contact us if you are considering outsourcing cell culture or cell manufacturing.

Quality test implementation system



H.U. Cells acts as the contact point and coordinates a meeting with quality test personnel at SRL regarding the test contents. Subsequently, we prepare an estimate and handle it with the contract. Quality testing is performed by the Biologics Research and Test Section of SRL, which communicates with customers in a timely manner and performs high-quality testing.

Laboratory test Quality test implementation System



The above flow and duration is just an example. It depends on the customer's development situation, the position of the requested test, and other factors.A standard operating procedure (measurement SOP) will be prepared for each test before it is conducted. The duration will vary depending on the time required for the content.In accordance with the Japanese Pharmacopoeia, we perform a product test after the preliminary test (validation test).

H.U.GROUP
H.U.Cells
H.U.Cells is a menmber of the H.U.group.

【Inquiries】
H.U.Cells, Inc.
050-2000-4558
hci.contact@hugp.com

Supporting your regenerative medicine development

that's GOOD science!®

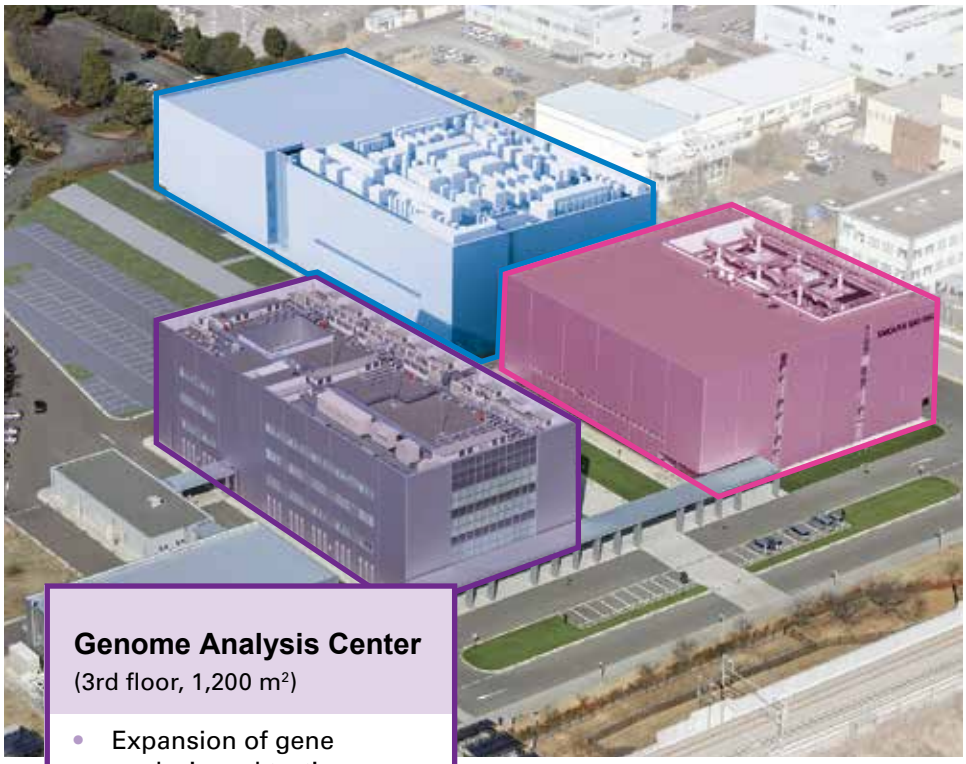
TaKaRa

Clontech TaKaRa cellartis

Partnering to develop your regenerative medicine products

Takara Bio offers high-quality, innovative tools and services to help research groups accelerate translational and clinical discoveries. We foster an environment of collaboration and innovation between our team members and the research community, providing custom solutions that address any stage of the gene and cell therapy development process.

As a contract manufacturing organization (CMO) that provides a variety of manufacturing services, Takara Bio is committed to understanding and meeting your quality needs and expectations. Our Center for Gene and Cell Processing (CGCP; established in 2014) is designed specifically for the safe, efficient manufacture of gene and cell therapy products. To accommodate the rapidly growing demand for gene and cell therapies, we have expanded our facilities and are continually enhancing our services for biopharmaceuticals and regenerative medicine products under Good Manufacturing Practice (GMP) and Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (GCTP) guidelines. In addition, we offer genetic analysis of your gene and cell therapy products in our nearby Main Research Building.



Genome Analysis Center
(3rd floor, 1,200 m^2)

- Expansion of gene analysis and testing

Center for Gene and Cell Processing II (CGCP II)
(14,500 m^2)

- Expansion of GMP vector production, aseptic filling, and quality testing facilities

Center for Gene and Cell Processing (CGCP)
(6,700 m^2)

- Plasmid and protein production
- Vector production
- Aseptic filling
- Quality testing
- Cell processing
- Cell bank storage

Life Innovation Center (LIC)

The LIC cell processing facility (located in Kawasaki, Kanagawa, Japan) began operations in April 2017, increasing our production capacity. At the LIC, we offer contracted cell processing services for stem cells and transgenic cells for clinical studies. We also utilize the LIC as our cell processing base for clinical trials in the Tokyo area.

A one-stop manufacturing facility that meets major regulatory requirements

Our GMP/GCTP facility enables us to manufacture your cell banks, viral vectors, and cell-based products in accordance with major GMP/GCTP regulations. With the addition of CGCP II, our facility is now capable of large-scale viral vector manufacturing, allowing us to offer production at various scales depending on your needs. We expanded and enhanced our Quality Control area to meet the requirements of various quality testing and characteristic analyses for regenerative medicine products. With our increased capacity and room for further expansion, we can provide complete support for your gene and cell therapy development, from research to clinical application and commercial production.

Designed for efficiency, purity, and high-quality production

- Operated in accordance with ISO 9001 and GMP for investigational products
  - Received accreditation as a "foreign cell processor" (Japan's Ministry of Health, Labour and Welfare, facility number FA5150002)
  - Awarded manufacturing and commercial licenses for regenerative medicine products in 2019
- Multiple manufacturing rooms enable the parallel manufacture of multiple items
- Air locks, one-way passage systems, independent ventilation systems, and separated flow for operations and materials minimize the risk of contamination

FOYA 2016
Facility of the Year Awards
CATEGORY WINNER
Facility Integration

An ISPE Facility of the Year winner

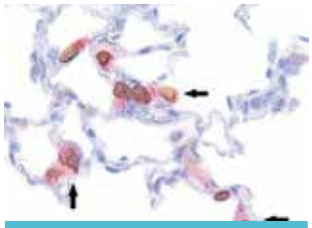
In 2016, the International Society for Pharmaceutical Engineering selected Takara Bio's CGCP as the winner of its Facility of the Year Award (in the Facility Integration category). Its unique environment ensures product safety and was determined by the judges to be a practical, efficient model for future biopharmaceutical facilities.

Complete support for your gene and cell therapy development

Your work is extremely important to us, and you can rest assured that we will treat your project as if it were our own. Our custom services include viral vector production, cell processing, clinical-grade human embryonic stem (hES) cell line derivation, quality testing, and cell banking. We employ single-use technologies, eliminating the need for time-consuming and costly cleaning and validation.

Process development

- Process optimization
- Scale-up studies
- Nonclinical batch manufacturing
- Safety and quality testing/ development

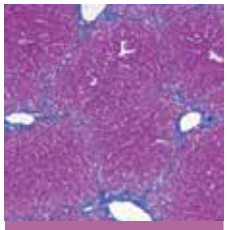


Preclinical studies (subcontract)

- Pharmacological testing
- Pharmacokinetic testing
- Toxicity testing
- Tumorigenicity testing

Investigational product manufacturing

- Viral vector production
- Cell banking
- Genetically modified cell manufacturing
- Cell processing
- Investigational drug storage and delivery
- Safety and quality testing
- Stability testing



On market

Exceptional quality standards provide confidence in your product

Takara Bio facilities adhere to stringent ISO 9001 and GMP guidelines, providing a strong foundation of trust in the quality of your product and the service performed. All projects are conducted by our staff of 350 and overseen by an integrated management team consisting of experts in viral and/or cell manufacturing, quality control, and quality assurance. Our specially qualified QA team ensures that all manufacturing and testing services meet our quality standards and comply with your requirements.

Developing your process

We offer a cohesive approach to process development, safety testing, and quality testing in order to manufacture your product according to GCTP and GMP guidelines for investigational drug manufacturing.

Process development workflow

A project manager with extensive knowledge and experience in clinical development and manufacturing will facilitate interactions between your group, the sales team, and our manufacturing team. Our integrated approach ensures frequent communication with Takara Bio subject matter experts who support the rapid, worry-free process. We are happy to accept on-site audits upon concluding a quality agreement.

Initial consultation
Under a confidentiality agreement, we will develop a manufacturing plan based on your samples, preferred manufacturing methods and formulations, and stability specifications.

Pilot lot manufacturing
We will perform small-scale and scale-up manufacturing tests using raw materials and manufacturing methods suitable for investigational drugs.

Safety and quality test development
We will create safety and quality tests based on your requirements, using the pilot lots created for your initial custom formulation.

Transfer and scale-up manufacturing (non-GMP)
We will transfer the manufacturing process to our GMP facility and manufacture non-GMP grade material at quarter- to full-scale.

Specification and characteristic testing
The non-GMP manufacturing samples created during transfer and scale-up are used for nonclinical tests and for safety/quality test validation.

Stability and transportation testing
The non-GMP manufacturing samples are also used to perform stability tests under your desired storage conditions. Transport tests can be performed upon request.

Cell banking

We offer cell banking services for producer cells (e.g., CHO and 293 cells) and human iPS and ES cells. We can provide Research Cell Banks, Master Cell Banks, and Working Cell Banks. Our CGCP facility can produce multiple batches in parallel, and we leverage our years of experience—for example, in developing and producing our RetroNectin® GMP grade (FDA DMF application number 18898)—in all of our services, including *E. coli* cell bank manufacturing, plasmid vector manufacturing, and quality testing.

Our cutting-edge facility is equipped with liquid nitrogen storage tanks and ultra-low-temperature freezers connected to a 24-hour monitoring system. Regardless of the cell type stored, you will receive a monthly report on the status of your cell bank.

Case study: manufacturing a 293 cell bank

Lead time: 9 months, including quality testing; varies with project scope

Cell processing under GMP conditions

Pilot manufacturing (non-GMP)

- After the product meets acceptance criteria, we expand the cells at a small scale and then at full scale to confirm the manufacturing process
- We confirm the cell proliferation profile

Manufacturing under GMP conditions

- We manufacture the cell bank in our GMP facility
- We deliver manufacturing plans, documents and reports, and 100–200 vials of cell bank with 3–5 x 10^6 cells/vial

Quality testing

Standard test items for 293 cells:

- Sterility
- *Mycoplasma*
- *In vitro* virus testing
- *In vivo* virus testing
- Transmission electron microscopy assay
- Reverse transcriptase assay (F-PERT)
- Cell viability
- Cell identification (RAPD-PCR)

Case study: manufacturing an *E. coli* cell bank

Lead time: 6 months, including quality testing; varies with project scope

Single-use, 200-L culture system

Pilot manufacturing (non-GMP)

- After the product meets acceptance criteria, we expand the cells at a small scale
- We confirm the cell proliferation profile and quality

Manufacturing under GMP conditions

- We manufacture the cell bank in our GMP facility
- We deliver manufacturing plans, documents and reports, and ~150 vials of cell bank

Quality testing

- Colony formation
- Auxotrophy
- Biochemical assays
- Microbial enumeration
- Plasmid retention rate
- Vector copy number
- Restriction enzyme digestion
- Plasmid sequencing
- Lysogeny
- Phenotype (UV sensitivity, antibiotic resistance, etc.)
- Test production (flask culture)

Cell processing

Our cell processing services provide you with gene and cell therapy products as well as expert support in entering the clinical market in Japan and other countries. Our services leverage the expertise we have built while developing novel products to support T-cell receptor (TCR) and chimeric antigen receptor (CAR) therapies. Our proprietary expertise includes techniques to efficiently transduce target genes using our gold-standard transduction enhancer, RetroNectin reagent, as well as abundant experience with closed culture systems.

Cell processing in a closed culture system

Case study: retroviral vector transduction of a cell line

Workflow timeline for retroviral vector transduction — *Time (months; varies with project scope)*

	3	6	9	12	15	18	21	24	27	30	33	36
Manufacturing virus producer cells												
Manufacturing and quality testing of producer cell bank												
Viral vector manufacturing (1st lot); quality testing												
Process development and evaluation of transduced cell line												
Pilot-lot test manufacturing of transduced cell line (non-GMP)												
Manufacturing of transduced cell line (1st lot); quality & stability testing												
Nonclinical studies												
Viral vector manufacturing (2nd lot); quality testing												→
Manufacturing of transduced cell line (2nd lot); quality testing												→

Standard tests* for CAR-T cells

If you are using viral transduction to develop a CAR-T therapy, we offer:

Verification tests	Infectious factor verification tests	Characteristic analyses
• Appearance test • Cell concentration • Cell viability • Target gene copy number • Vector integrity test (PCR) • LAM-PCR	• Sterility • *Mycoplasma* • Endotoxin • Replication-competent virus • *In vitro* virus testing • GaLV RCR testing	• IL-2 dependent proliferative study • Immunophenotyping • CAR expression • Cytotoxic activity

*Not including virus quality testing

Viral vector production

We have over 10 years of experience in viral vector production and a track record of over 100 virus and cell-bank production projects that were manufactured and tested in accordance with GMP guidelines. We offer virus production services for:

- Retrovirus
- Lentivirus
- Adenovirus
- Adeno-associated virus
- Herpes simplex virus
- Sendai virus

Automated filling system

Adeno-associated virus (AAV) vector production

AAV vectors can transduce into proliferating cells and can impart long-term expression. Furthermore, AAV has little immunogenicity. For these reasons, AAV vectors are getting increasing levels of interest for use in gene therapy. As each serotype shows different characteristics and tissue specificity, AAV vectors are expected to transduce target genes efficiently into heart, liver, muscle, retina, and the central nervous system.

Case study: AAV vector production

Workflow timeline for AAV vector production — *Time (months; varies with project scope)*

	3	6	9	12	15	18	21	24	27	30	33	36
Plasmid vector production; quality testing												
Master Cell Bank manufacturing; quality testing												
Process development/test manufacturing												
Viral vector manufacturing (1st lot); quality testing												
Preclinical testing												
Viral vector manufacturing (2nd lot); quality testing												→

Examples of standard tests for an AAV vector

Verification tests	Purity tests	Safety tests
• Properties • pH determination • Target gene/protein expression • Vector sequence • Viral titer	• Protein concentration • Capsid rate • Residual host DNA/protein • Residual benzonase nuclease • Residual plasmid	• Sterility • *Mycoplasma* • Endotoxin • Replication-competent virus • *In vitro* virus testing

Retroviral and lentiviral vector production

Retroviral and lentiviral vectors are widely used for gene transduction of mammalian cells, including hematopoietic stem cells, and are powerful tools for gene delivery. With our experience in clinical research, we provide viral vectors for developing genetically modified cells for *ex vivo* gene therapy.

Liquid chromatography apparatus

Quality testing

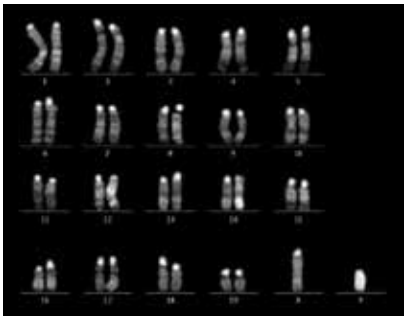
We provide testing to evaluate the quality of your cell products for use in regenerative medicine. Our quality testing services are compliant with international regulations (such as FDA, ICH, CFR, and USP) and with Japanese Pharmacopoeia (JP). These services can be included as a part of product evaluations, process tests, and stability tests necessary for product release.

Safety testing

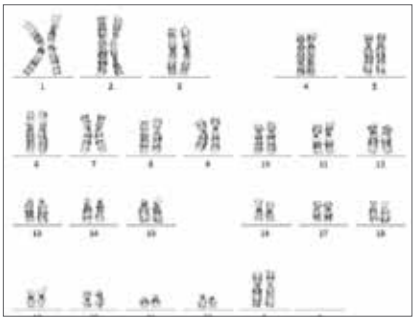
We offer Quality Control testing for cell and tissue products (and their raw materials) at various levels of stringency from GMP-compliant to simple, quick, and cost-effective tests for non-GMP-grade materials.

Typical safety tests

	For GMP-grade materials	For non-GMP-grade materials
Sterility	• Direct inoculation method (JP) • Membrane filtration method (JP) • Rapid microbial detection method (JP)	Gas measurement
Endotoxin	Kinetic turbidimetric method (JP)	Real-time PCR
Mycoplasma	Culture method, DNA staining method, real-time PCR (JP)	Real-time PCR
Human viruses	High-sensitivity detection by real-time PCR; target viruses: HIV-1, HIV-2, HBV, HCV, HTLV1&2, ParvoB19, EBV, CMV, WNV	Real-time PCR (for six or nine kinds of human viruses)
Chromosomal analysis	Please contact us for more information	G-band analysis, Q-band analysis (FISH or multicolor FISH is also available)



Q-band karyotyping of a mouse ES cell (40, XY)



G-band karyotyping of a human iPS cell (46, XY)

Purity testing

We know that the purity of your final product is critical. We provide both residual purity testing and cell purity validation to ensure that your cellular product is free of contaminating cell types and impurities from the manufacturing process.

Purity tests for cellular products	
Residual purity tests	We check for residual impurities from the manufacturing process that may remain in the final product, such as bovine serum albumin, cytokines, and viral vectors.
Cell purity validation	We use immunostaining with cell surface markers to detect cells with unintended characteristics.

Cellular analysis

We offer various cellular analysis tests to evaluate the quality of your products for use in regenerative medicine. We leverage our extensive analysis techniques such as cell immunophenotyping, cytokine production assays, cytoxicity and proliferative responsiveness assays, and next-generation sequencing.

Cellular analysis tests	
Immunophenotype analysis	We use flow cytometry to characterize the cell-surface antigen or intracellular antigen of target cells to identify specific cell types in a heterogeneous population.
Cytokine analysis	We use flow cytometry to determine which cytokines are produced in the target cells in response to peptide stimulation.
Protein measurement	We use ELISA to measure cytokines and growth factors in serum and cell culture supernatant.
Cytotoxicity assays	We measure natural killer (NK) cell activity in peripheral blood cells and cultured cells, as well as cytotoxicity in response to tumor peptide antigens and tumor antigen cell lines.
Cell proliferation	We use MTT and WST1 assays to measure lymphocyte and general cell proliferation.
Repertoire analysis	We use NGS assays to measure the diversity of the TCR and BCR repertoires.
Gene copy number	We measure target gene copy number using real-time PCR to detect proviruses.
Genome mutations	We use the latest genome analysis techniques to evaluate chromosome structure and copy number and to identify mutations.
Clonality analysis	We confirm the absence of neoplastic clones by analyzing the integration site in the host genome of genetically modified cells by LAM-PCR.

Cancer immunotherapy

Takara Bio Inc. (the parent company of the Takara Bio Group) has made exciting advances in engineered T-cell therapies (currently in clinical development). We apply this same expertise in cell culture, differentiation, and process development for GMP-grade manufacturing to your projects. Typical services include:

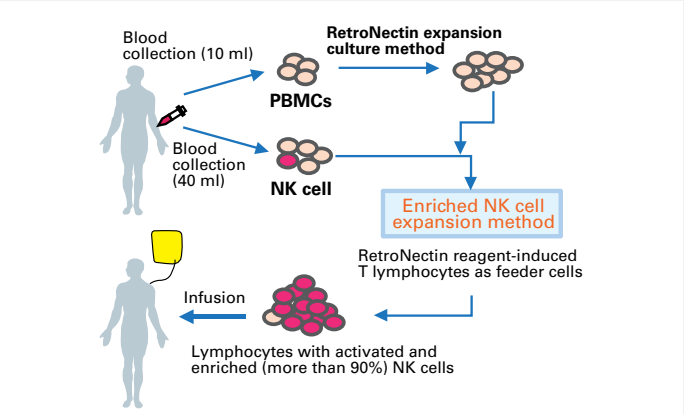
- Expansion of suspension cells in a closed system
- Expansion of adherent cells in a multilayer chamber
- Generation of Research Cell Bank for GMP process development
- Manufacturing of cell bank from tissue
- Manufacturing of Master Cell Bank from Research Cell Bank

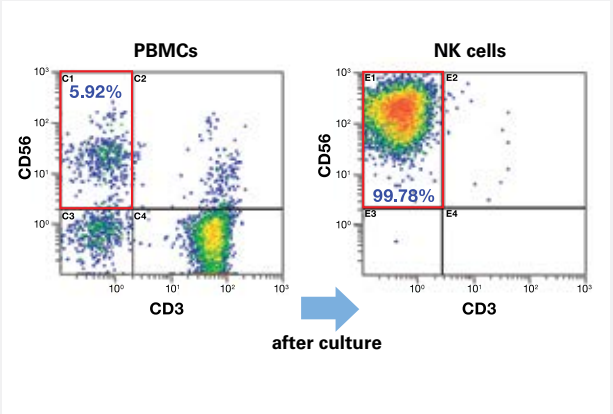
Your cells, our skills

Our services provide you with gene and cell therapy products as well as expert support in entering the clinical market in Japan and other countries. Our team is highly skilled in cell-culture techniques and technologies, as well as operational scale-up to large-volume cell culture bags. We are experts in handling RetroNectin reagent-induced T lymphocytes, dendritic cells, NK cells, cytotoxic T lymphocytes, and activated lymphocytes.

Case study: enriching activated NK cells

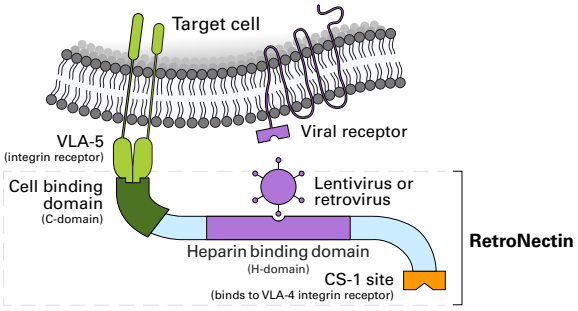
We created the original technology to expand enriched high-activity NK cells at large scale by culturing with RetroNectin reagent-induced T lymphocytes, peripheral blood mononuclear cells (PBMCs), and OK432 (Picibanil). With our technology, 6 x 10^9 NK-enriched cells can be obtained from 40–50 ml of blood.





Enhance gene transfer and T-cell expansion with RetroNectin reagent

RetroNectin reagent is a recombinant human fibronectin fragment that can enhance retro/lentiviral-mediated gene transfer to mammalian cells expressing integrin receptors VLA-5 and VLA-4. T cells are typically expanded in the presence of interleukin-2 (IL-2) by stimulation with anti-CD3 antibody. The addition of RetroNectin reagent in this stimulation step dramatically increases the efficiency of T-cell expansion.



We are scientists who strive to help other scientists

Your innovative ideas have no boundaries when backed by our services. We can support your entire workflow, from cell banking and vector construction to process development, investigational drug manufacturing under GCTP and GMP guidelines, and regulatory support. Let our expertise facilitate your exploration of health.

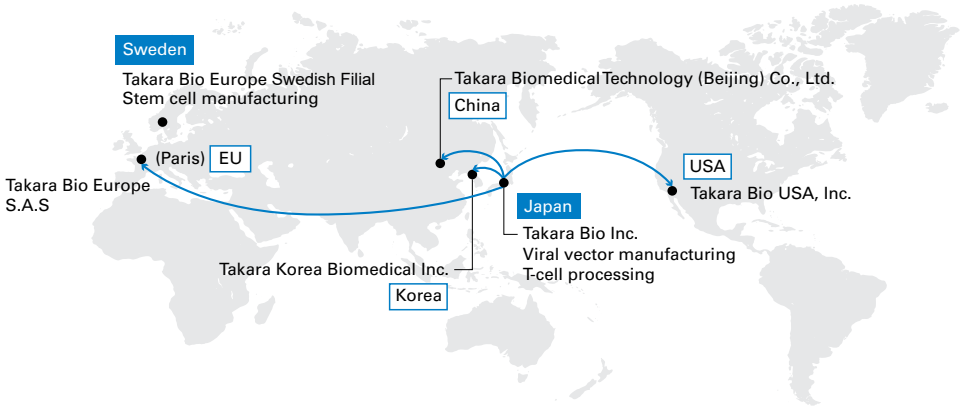
Applying our expertise to your projects

As a group of companies with a mission to improve quality of life through biotechnology, we provide tools and support for basic, translational, and clinical research across many areas of interest. Takara Bio Inc. has made exciting advances in gene therapy technologies and uses a focused strategy for accelerating products to market. Takara Bio Inc. carefully selects development projects for which they will complete all steps up to applying for approval, while also accelerating development of therapies by conducting joint projects with outside partners. The same expertise applied to these ongoing clinical development projects can be applied to your project:

Therapeutic approach	Takara Bio Inc. project	Disease targeted
Engineered T-cell therapies	JAK/STAT CAR-T therapy	B-cell Lymphoma, CLL/SLL
	siTCR™ gene therapy	Synovial sarcoma

A global network, at your service

Our CMO services leverage Takara Bio subject matter experts and affiliates located across the globe. Facilities and personnel in Japan support viral vector production, T-cell processing, and quality-testing services, while facilities and personnel in Sweden support Cellartis® Human Pluripotent Stem Cell Services, which include clinical-grade human embryonic stem (hES) cell line derivation, banking, sourcing, reprogramming, and differentiation.



NOTE: *The workflow and timing of your project may differ from the examples described in this brochure, depending on your target gene, process development needs, production scale, and required number of lots.*

Learn more:

takarabio.com/cmo-services
takara-bio.com/medi_e/index.html

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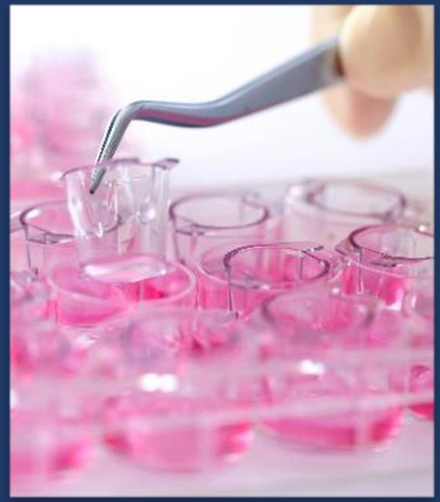


Human Chemistry, Human Solutions TEIJIN

Teijin Group: Value maximization of Cell & Gene Therapy including Regenerative Medicines in Japan

Regenerative Medicine Business Strategy Dept.
Regenerative Medicine & Implantable Medical Device Div.
TEIJIN LIMITED

October 2023

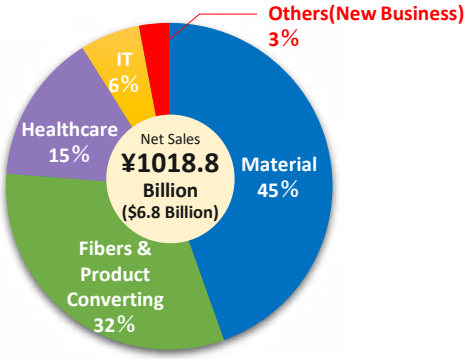
About Teijin Group:
Offering various innovative solutions including healthcare

About Teijin

Company Name	TEIJIN LIMITED
Found	1918
Tokyo HQ	Kasumigaseki Common Gate West Tower, 2-1, Kasumigaseki 3-chome, Chiyoda-ku, Tokyo, Japan
Representative	President and CEO, Representative Director of the Board: Akimoto Uchikawa
Stock code	3401 (Tokyo stock exchange, PRIME)
Group Companies*	169 (Japan 52, Overseas 117)
Group Employees*	22,864 (Japan 9,564, Overseas 12,890)

*as of Mar 31, 2023

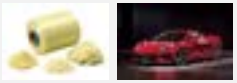
FY2023 Annual Sales



Our Philosophy

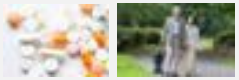
Business Domain & Earnings Structure

Materials



- High-performance materials
- Composite molding materials

Healthcare



- Pharmaceuticals Home healthcare
- Functional foods

Fibers & Product Converting

- Fibers & Product Converting

IT

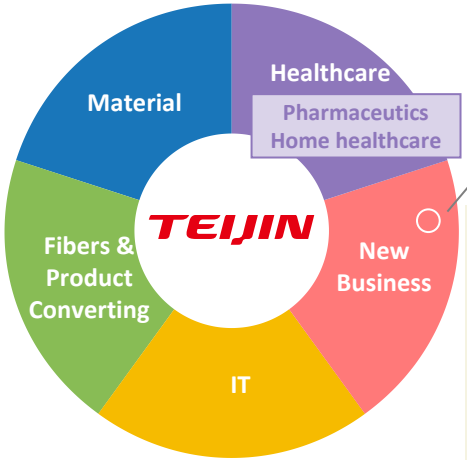
- IT

New Business

- Engineering Business
- Regenerative Medicine
- Implantable Medical Products

Teijin Group Business in Cell & Gene Therapy (CGT) & Regenerative Medicine (RM)

- Our corporate philosophy is to improve “Quality of Life”, and to be a company that supports the society of the future
- Based on material and healthcare business, expand our business into regenerative medicine (CGT & RM).



New Business Development Unit

BD function

Regenerative Medicine & Implantable Medical Device Div.

- Maximize synergies within the Teijin Group in the regenerative medicine business and implantable medical device business
- Building a foundation that will become Teijin's new backbone business

Regenerative Medicine (Cell & Gene therapy)

Implantable Medical Device

Regenerative Medicine Business Strategy Dept.

TEIJIN REGENET CO., LTD. TEIJIN REGENET

J-TEC Japan Tissue Engineering

Teijin Nakashima Medical

Teijin Medical Technologies

R&D function

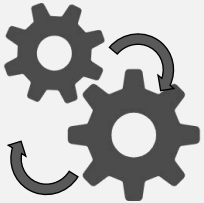
BD function

Business Development	CDMO of CGT & RM	CDMO of CGT & RM	MAH of CGT & RM

Cooperation

Our Vision : Contribution to Cell and Gene Therapy

Establishment of CGT & RM eco system



Functional integration by Industry-Academia-Government collaboration to provide whole services

Utilizing the high quality and speedy development system of the Kashiwa-no-ha platform,
we aim to create a society where CGT & RM is possible not only in Japan but throughout Asia.

New business model based on “Manufacturing Technology”

Offering supports of product design, process development, and scale up to commercialize good seeds

Provide globally accepted manufacturing with a balance of science and QCD (high quality/low cost/short lead time)

Globalization

Supports of global market expansion of Japan-origin seeds, and entry of global seeds into Japan

Contributing to the expansion of CGT & RM business and market into US/EU by Japanese and APAC.

Contribution to societies and patients through CGT & RM services

Teijin provides new treatment, CGT & RM, for unresolved diseases
and contribute to market expansion.

Teijin Group's Facility

- Unique facilities that satisfy needs per various modalities and development stages (Chiba, Yamaguchi, Aichi)
- Seamless transfer from R&D to commercial is enabled by sharing technologies, know-hows, and skilled personnel between the sites

TEIJIN REGENET

Kashiwa-no-ha Facility

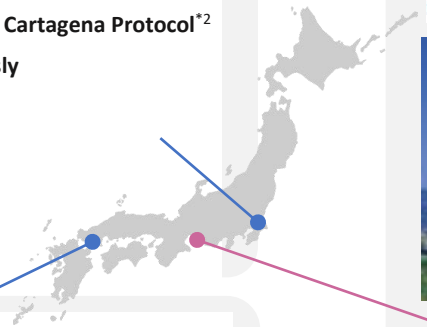
Facility area: **800** m², **4** suites
Compliant: Clinical GMP, RM Act*3, Cartagena Protocol*2
10 projects conduct simultaneously

- Operation from Feb. 2024
- Utilize of Kashiwa-no-ha RM PF, industry-academia collaboration
- In-facility collaboration with TFBS
- Participation of J-TEC employees

Iwakuni Factory

Facility area: **2,400** m² , **10** suites(max.)
Compliant: GMP (GCTP*1), Cartagena Protocol*2
3 to **6** products manufacturing simultaneously

- Personnel with experience in pharmaceutical GMP production and CMC
- Co-creation with engineer specializing in healthcare
- Highly convenient and expandable location close to airports and stations
- Started trial for commercial manufacturing of CAR-T product



J-TEC

J-TEC (Gamagori)

Facility area: **5,500** m²
Compliant: GCTP*1, RM Act*3

- A track record of manufacturing and supply over 2,000 products
- More than 13 CDMO contracts

*1 GCTP: Good Gene, Cellular, and Tissue-based Products Manufacturing Practice
*2 The Cartagena Protocol is to ensure the safe handling, transport and use of living modified organisms that may have adverse effects on biological diversity, taking also into account risks to human health. Japan adopted it in 2000.
*3 RM Act: Act on the Safety of Regenerative Medicine (regulation for non-GCP clinical research and treatment without health insurance coverage)

Teijin group's alliance with external partners

Supports for expansion to US

RESILIENCE

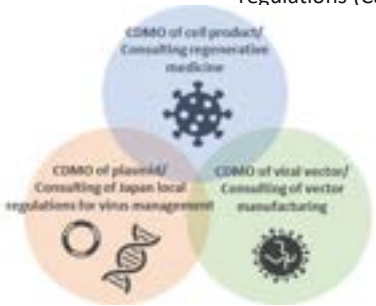
- Manufacturing/referral partnership in North America
- Technical partnership
- Manufacturing Viral vector

MediRidge

- Manufacturing plasmid
- Consulting on Japanese regulations (Cartagena Law)

国立がん研究センター
National Cancer Center Japan

- Selection of target diseases and patients
- Clinical trial planning support
- Conducting clinical trials and research



Plasmid & viral vector manufacturing

tfbs

- Referral partnership
- Manufacturing viral vector

三井不動産
MITSUI FUDOSAN

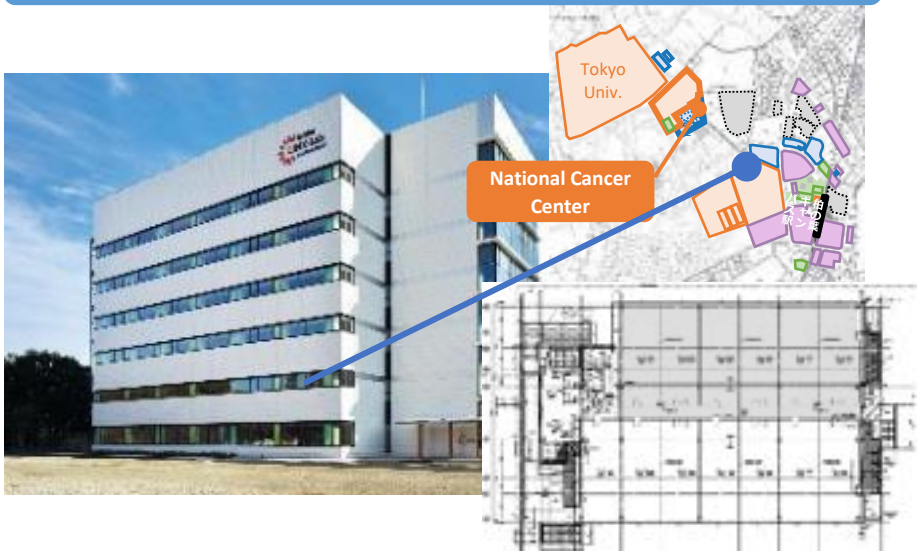
- Operation Kashiwa-no-ha RM PF and Kashiwa-no-ha Smart City
- Cooperation with LINK-J

Development platform for Cell & Gene Therapy

Overview of TEIJIN REJENET Kashiwa-no-ha Facility

- **Collaboration:** Located at Kashiwa-no-ha campus in Chiba, near by Tokyo Univ. Chiba Univ. and national research institutes.
  Approx. half of the 2nd floor of Link Lab Kashiwa-no-ha, adjacent to the National Cancer Center East Hospital.
- **Flexibility:** Clean room area and 4 CPCs in 800 m² area of the floor
  Facility design is "flexible" and "compact"
- **Network:** Collaboration with group company J-TEC such as assignment of skilled people and sharing of know-hows
  Process/test method development and global expansion utilizing collaboration with TFBS/MediRidge and Resilience

Mitsui Link-lab. Kashiwa-no-ha



Facility Overview

- Facility area: **800** m²
- CPC: **4** rooms
- Warehouse: **2** rooms
- Lab room: **1** room
- Compliant: Clinical GMP, RM Act, Cartagena Protocol
- More than **10** pjs conduct simultaneously

Equipment of TEIJIN REJENET Kashiwa-no-ha Facility

Manufacturing

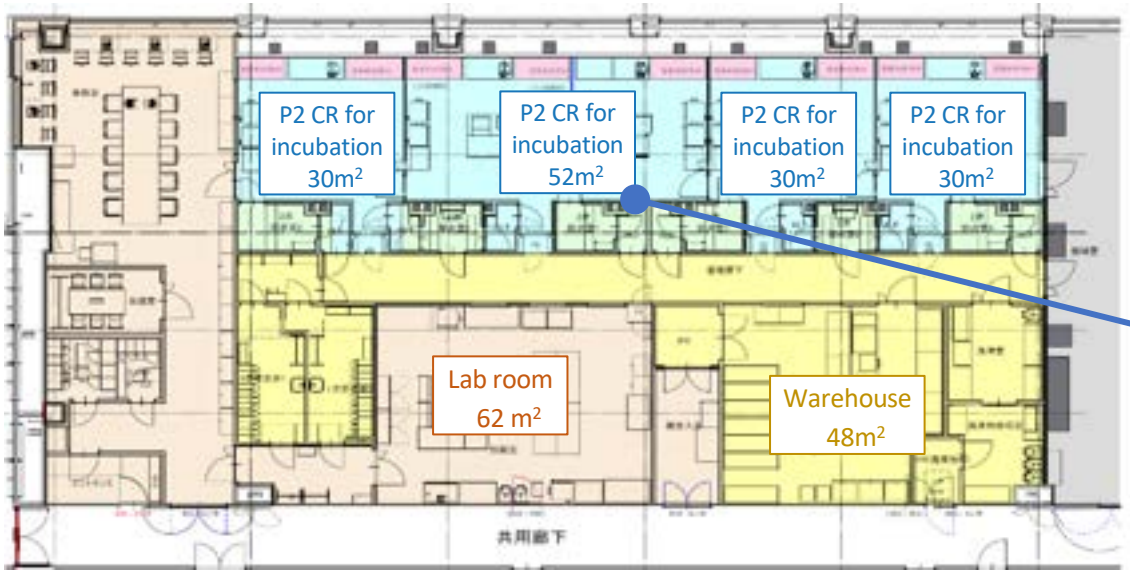
General equipment for cell manufacturing

- 7 Safety cabinets
- 9 CO_2 incubators
- Centrifuge
- Microscope
- Deep freezer

Equipment can be installed according to client's requests

Analytics

- Flow cytometer
- Plate reader
- Rt-qPCR
- Toxinometer etc.



P2 Clean room for incubation

Features of TEIJIN REJENET Kashiwa-no-ha Facility: Kashiwa-no-ha Regenerative Medicine Platform (RMPF)

As a core function of the Kashiwa-no-ha RMPF, TEIJIN will collaborate with the National Cancer Center and Mitsui Fudosan to contribute to solving problems in the practical application of CGT & RM seeds.

TEIJIN
TEIJIN REGENET CO., LTD.
J-TEC

TEIJIN REJENET Kashiwa-no-ha Facility

- Product development, clinical supply
- Supports for commercialization

Seeds from Academia/Biotech

Clinical/ Analytical CROs, — Join

Hospitals, Medical Institutes — Join

Join — Pharma

Join — Venture Capitals

Kashiwa-no-ha Regenerative Medicine Platform
Mitsui Fudousan
(Real-estate company, office function)

Join/Collaboration

Innovative Treatments

Commercialization

Patients, Hospitals

GCT & RM Market

National Cancer Center (NCC)

- Medical supports as KOLs
- Initiation of clinical researches/trials

国立がん研究センター
National Cancer Center Japan

Overview of TEIJIN REJENET Iwakuni Factory

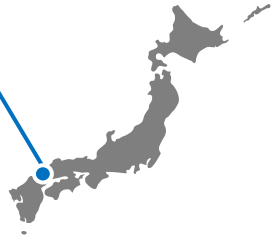
- **Equipped Facilities:** Clean room area and 10 CPCs(max.) in 2,400 m² area of the floor
  Integrated manufacturing system from clinical supply to commercial supply
  Can satisfy a wide range of needs such as transduction, cell culture, tissue culture, etc.
- **Skilled Experts:** Experience in J-TEC's cell technology field, experience in CAR-T manufacturing
  Experts with diverse experience in GMP, cGMP, QMS, healthcare specialized engineering, etc.
- **Location:** Highly convenient close to airports and stations and expandable

Iwakuni Factory

Factory Overview

- Facility area : **2,400** m²
- CPC : **10** rooms(max)
- Warehouse : **8** rooms
- QC lab : **2** rooms(max)
- Lab room : **1** rooms
- Compliant : GMP (GCTP), Cartagena Protocol
- **3** to **6** products manufacturing simultaneously

Floor Plan of TEIJIN REJENET Iwakuni Factory



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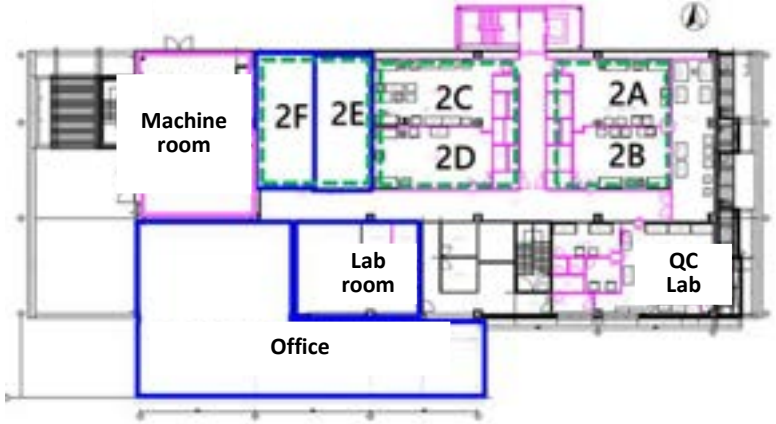
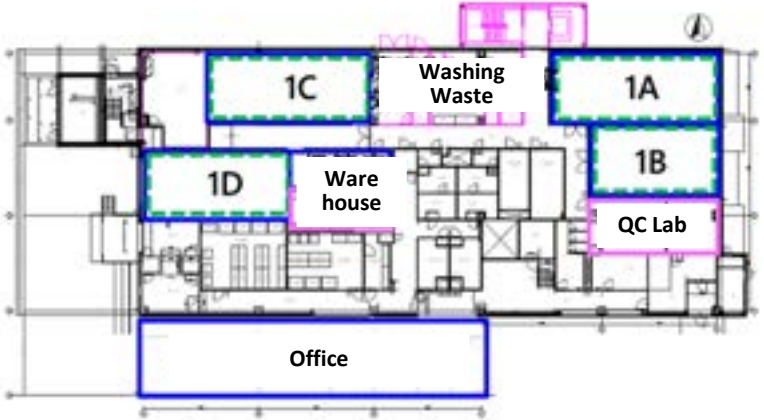


Room	Area
2A	43 m²
2B	48 m²
2C	57 m²
2D	51 m²
2E	44 m²
2F	44 m²

Occupied

1F



Room	Area
1A	43 m²
1B	65 m²
1C	61 m²
1D	53 m²

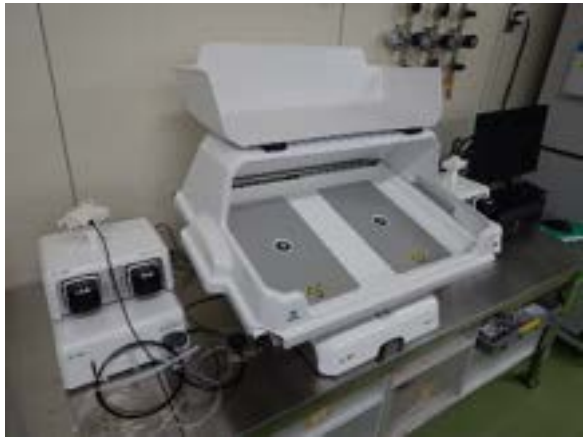
Equipment of TEIJIN REJENET Iwakuni Factory

Manufacturing

- Safety cabinets
- CO_2 incubators
- Centrifuge
- Microscope
- Deep freezer
- Cell wash (LOVO)
- Closed automated cell preparation system (Sepax)
- Cell culture system (Xuri) etc…

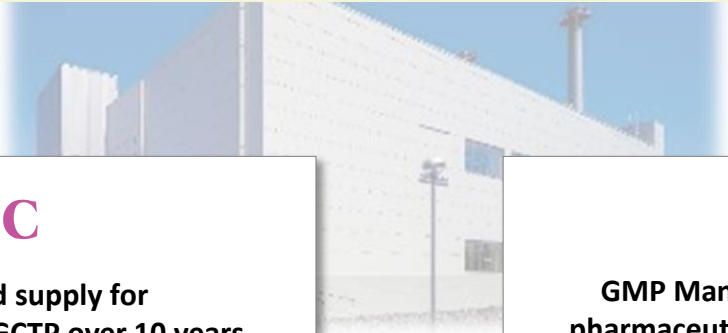
Analytics

- Flow cytometer
- Plate reader
- Rt-qPCR
- Cell counter
- Gel imaging system
- Fully automatic microbial culture detection device (BacteAlert)
- Cryogenic module for BacteAlert



Features of TEIJIN REJENET Iwakuni Factory: Fusion of Strength

Our Iwakuni factory is a main CMO business base where the experience and know-how of J-TEC and Teijin/Teijin Pharma are integrated.



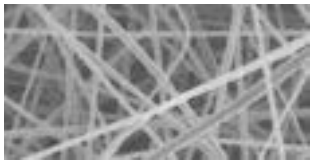
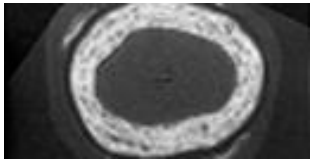
J-TEC

Stable manufacturing and supply for autologous cell products under GCTP over 10 years




TEIJIN

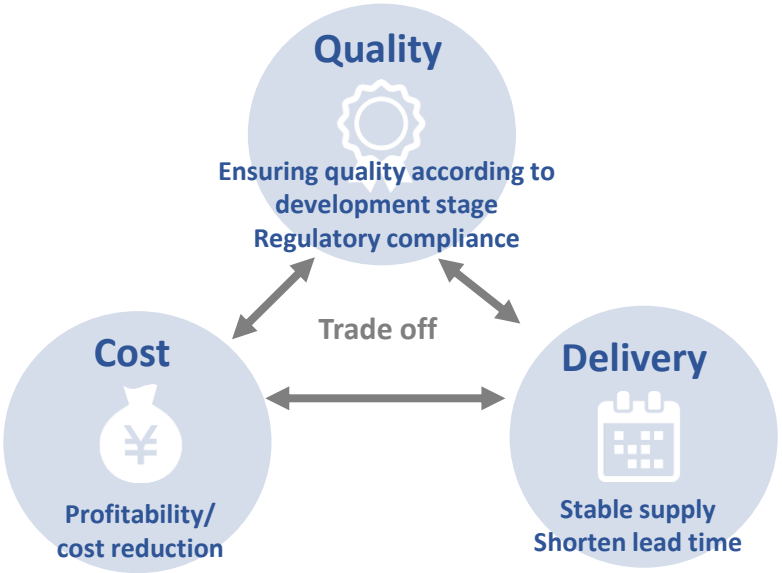
GMP Manufacturing/inspection experiences in pharmaceutical and medical products over 30 years

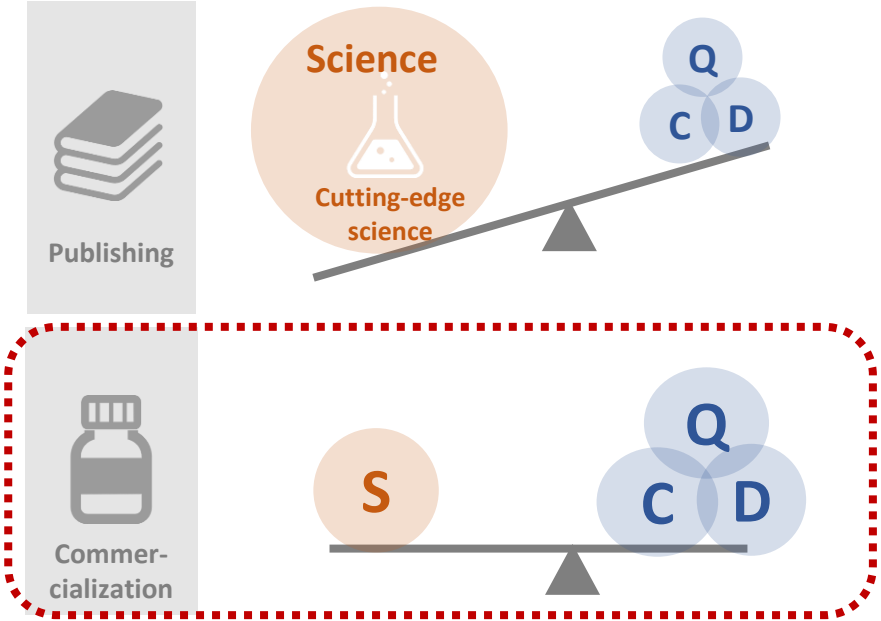

Teijin Group CDMO's efforts towards practical application of seeds

- **QCD (Quality, Cost, Delivery) are important factors** to develop high-quality products in a short time with low costs.
- In R&D stage in academia, **cutting-edge science (S)** is an also important factor.
- It is desirable to determine **optimal balance of QCD+S** depending on the goal.
  - ➡ Primary focus should be science if a goal is publishing a paper, but if aiming for commercialization, QCD should be also essential.

QCD （Quality, Cost, Delivery）



Balance of QCD+S (Science)



Teijin Group CDMO services and solutions

- Support for the development of products using the know-how and experience of Teijin Group (J-TEC, Teijin Pharma, etc.)
- Provide one stop service from early stage to launch by utilizing Teijin's value chain and partherships
- Beyond process development and manufacturing, multiple supports depend on the development stage

Seeds → R&D → Process Dev. Manufacturing → Non-clinical (Safety) → Clinical → Exit

One Stop Services from early stage to launch

Strategic support

- Target indication/Commercialization, marketability
- Support for expansion into abroad
- Gap analysis
- Planning regulatory strategy (Quality, Clinical)

Manufacturing /Analytics

- Product Design
- Process/ analytical development
- Support NDA, inquiry, inspection
- Manufacturing CTM/commercial product
- Planning manufacturing /analytical strategy
- Mnf. Non-clinical
- Specification, Characterization
- Procurement raw materials and viral vector
- Establish supply chain, transportation
- Support Cartagena

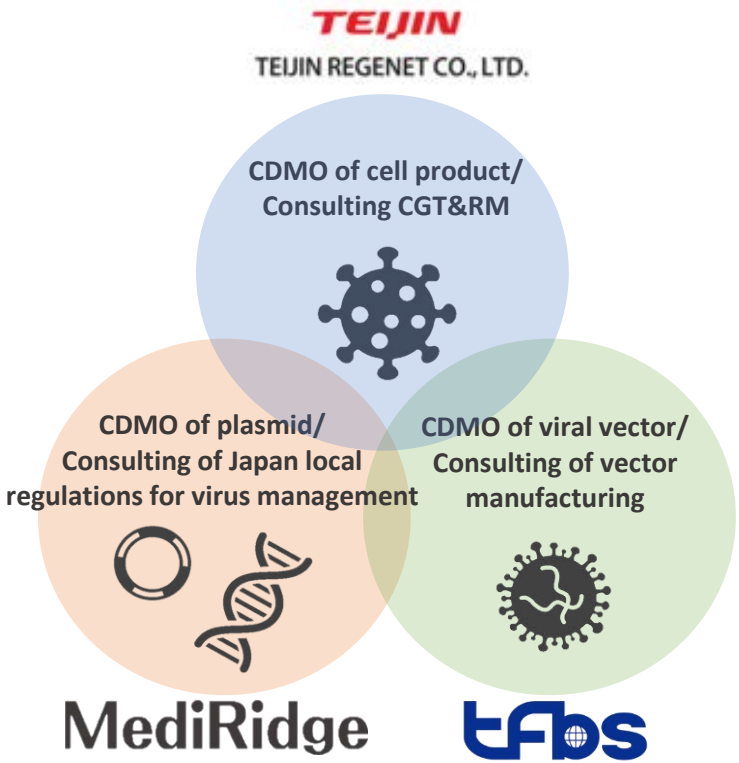
Clinical support

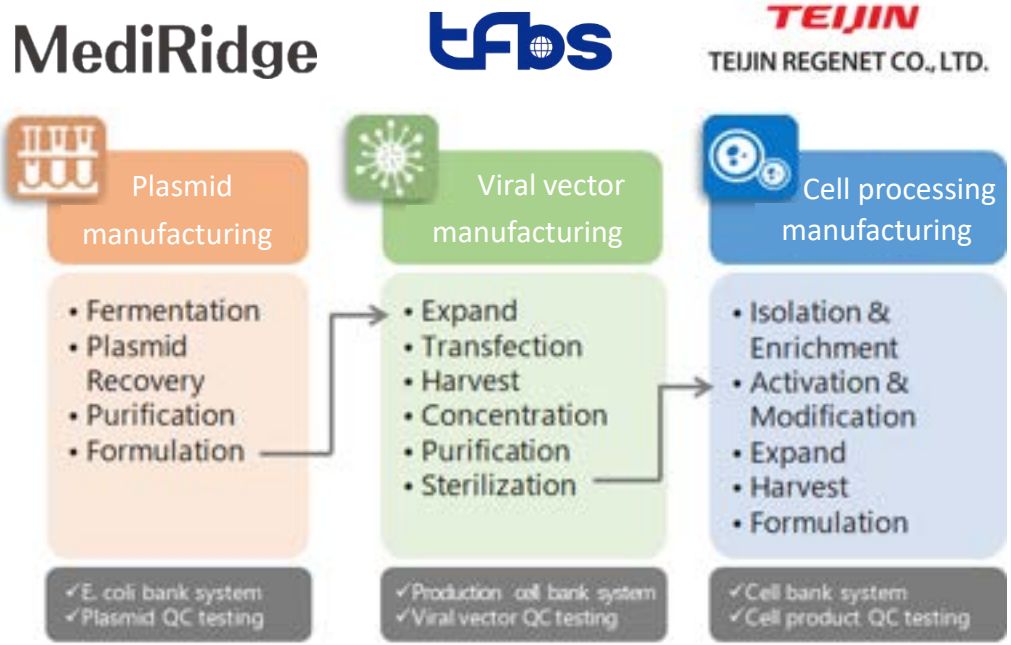
- Planning Dev. Strategy
- Clinical planning
- Non-clinical planning
- Non-clinical*
- Support for preparing application dossier

*in vitro testing

Alliance with TFBS/MediRidge: Viral vector/Plasmid supply

- Business partnership agreement with TFBS (Taiwan) and MediRidge is for the supply of viral vector.
- Utilizing the partnership in Taiwan, close to Japan, realize to on-time supply viral vector which are highly needs from clients.
- Utilize MediRidge's consulting functions for Japanese regulations (Cartagena)





Alliance with TFBS/MediRidge: Viral vector/Plasmid supply

TEIJIN

tfbs

- Taiwan's first GMP-compliant viral vector CDMO service One-stop GLP testing service from test method development,
- Provides clinical sample analysis, etc.

1. Short lead time to production
   Friendly to start up and academic customers
   Consultation included service
2. Flexibility
   Customized to the needs for budget, production volume, timeline, and regulatory requirement
3. One-stop-shop service
   From vector design, vector manufacturing, QC testing, assay development, animal studies for pharmacology and safety, to sample analysis of clinical trial
4. Goal-oriented project management
   Problem solving and cost consciousness

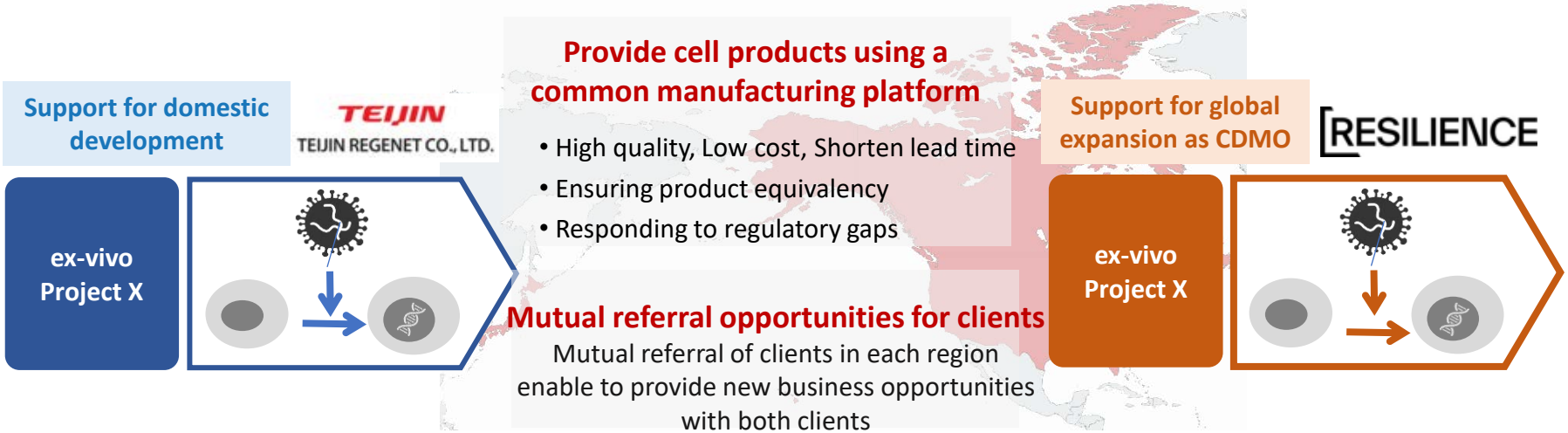
MediRidge

- Development and contract manufacturing of gene cell therapy and biopharmaceuticals, safety testing of viruses, etc., and consulting
- Responsible for plasmid CDMO service and TFBS distributor in Japan

1. As a CRO
   Virus safety testing for biopharmaceuticals, regenerative medicine products, raw materials for clinical research
2. As a CMO
   Plasmid production, cell bank construction, etc.
3. Research support consignment service
   Development of consulting on Japanese regulations (Cartagena Law)
4. TFBS distributor in Japan

Alliance with Resilience：Providing globally accepted cell therapy products

- Business partnership agreement with RESILIENCE (US) is executed to realize innovative treatments through manufacturing
- Provide products can be expanded globally through "global manufacturing" utilizing manufacturing platform built by RESILIENCE.
  1) Well-balanced QCD, 2) Ensuring product equivalency, and 3) Responding to regulatory gaps.



Common Values: Achieving Innovative Medicine Through “Manufacturing"

Development from design, work together with clients	Collaboration with Academia Teijin/NCC, RESILIENCE/Mayo Clinic/MD Anderson	Established manufacturing platforms, Close communication with regulatory authorities

Alliance with Resilience：Providing globally accepted cell therapy products

RESILIENCE

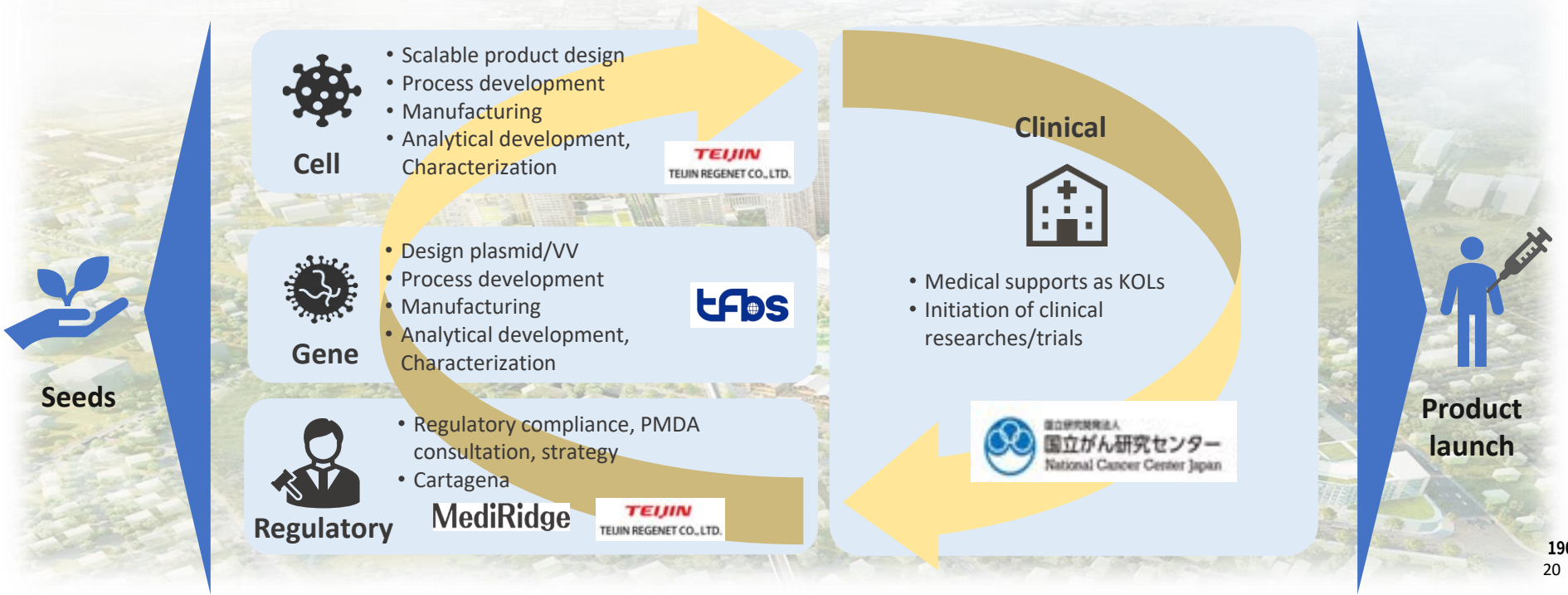
- 11 facilities for 5 modalities (cell therapy, gene therapy, nucleic acid medicine, protein/antibody, and vaccine)
- In CGT field, currently specialize in the cancer immunology field (CAR-T, etc.), and plan to expand into iPS etc. in the future.
- Build a scheme that combines unique technologies like "Lego blocks" to provide customers with the optimal technology. Build a new platform that integrates existing technologies incorporates DX to reduce time and costs. commit to innovation
- Formed partnerships with highly advanced medical institutions such as MD Anderson and Mayo Clinic, playing a central role in industry-academia collaboration platform

Company Name	National RESILIENCE, Inc （HP）
Found	Nov 23, 2020
HQ	9310 Athena Circle Suite 130 La Jolla, CA 92037, USA
Representative	CEO: Rahul Singhvi
Employees	About 2000 (as of Dec 2022)
Facilities/Sites	11

Ideal collaboration scheme to solve problems of CGT & RM seeds

- Seed developers need to **work closely with various stakeholders to solve problems through trial and error.**
  ➡ While **multifaceted collaboration with various partners is important**, it can sometimes be a heavy burden.

Kashiwa-no-ha RM PF: Accumulate solutions covering a series of value chains in Kashiwa-no-ha Smart City
Established supporting system for development of CGT & RM, including business alliances with TFBS (Taiwan) and MediRidge



Providing globally accepted CGT & RM products starting from APAC

- **Contribute to accelerate CGT & RM product development in Japan/APAC** by utilizing the Kashiwa-no-ha RM PF
- **Seamless global expansion/introduction support** collaboration with global strategic partners
  Providing products with "global manufacturing" **using manufacturing platform established by RESILIENCE**
- Support for global expansion and introduction not only as CDMO by utilizing Teijin Group's MAH such as J-TEC and Teijin Pharma.

TEIJIN

TEIJIN REGENET CO., LTD.

- High quality and agile development using Kashiwa-no-ha RM PF
- Aim to be a **development base in APAC** not only in Japan

Support for global expansion

Provide cell products using a common manufacturing platform

- High quality, Low cost, Shorten lead time
- Ensuring product equivalency
- Responding to regulatory gaps

Support for introduction to Japan/APAC

- Utilizing Teijin Group's MAH (J-TEC, Teijin Pharma)

RESILIENCE

- Smooth clinical trial implementation through collaboration with MD Anderson and Mayo Clinic

TEIJIN

TEIJIN REGENET CO., LTD.

Our CGT CDMO service is based on the assets
Teijin has cultivated over many years.
We will be a hub for social implementation of
Cell & Gene Therapy and Regenerative Medicine.

To deliver CGT & RM product to everyone
who needs it as soon as possible.

Speed up for Cell & gene therapy and Regenerative Medicine
Global solution provider for CGT&RM

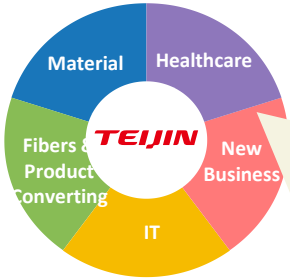
Web site：https://www.teijin-cdmo.com/

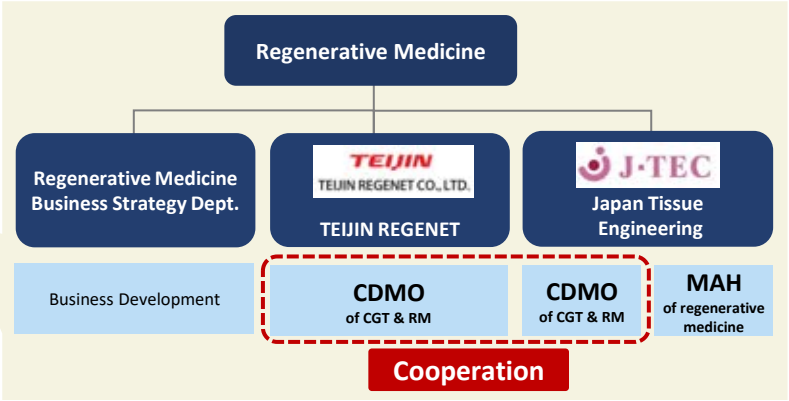
Short version（2-type）

Teijin Group Business in Cell & Gene Therapy (CGT) & Regenerative Medicine (RM)

Our Business

- CDMO services for CGT&RM
  - Product design, process/analytical development
  - CTMs/commercial manufacturing
  - Specification and characterization
  - Support NDA
- MAH for regenerative medicine (J-TEC)
- Development and sales for R&D Support product (J-TEC)

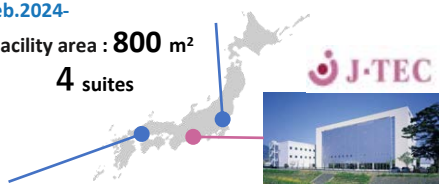




Our Facility

TEIJIN REGENET CO., LTD.

Kashiwa-no-ha Facility (Chiba)
Feb.2024-
Facility area : **800** m²
4 suites



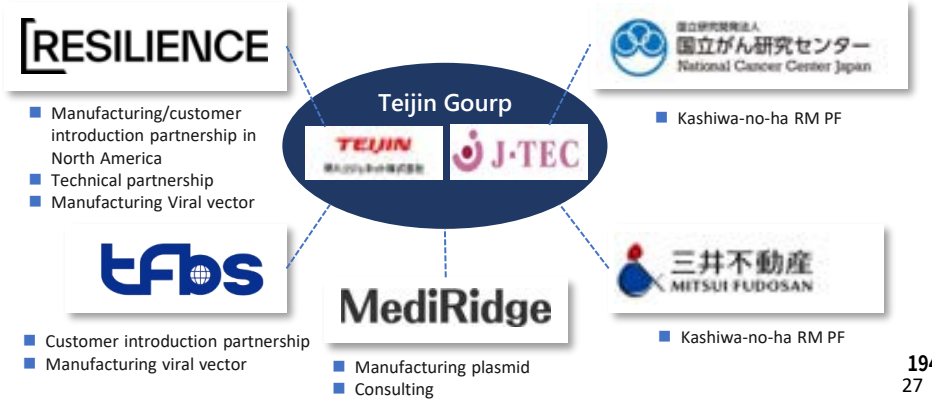
J-TEC

J-TEC（Aichi）
In operation
Facility area ：**5,500** m²

TEIJIN REGENET CO., LTD.

Iwakuni Factory (Yamaguchi)
Jul.2024-
Facility area : **2,400** m²
10 suites(max)

Strategic Alliance



Teijin Group Business in Cell & Gene Therapy (CGT) & Regenerative Medicine (RM)

Provide one stop service from early stage to launch and Multiple support depend on the development stage

Who We Are

- Based on material and healthcare business, expand our business into CGT&RM.
- In Mar. '21, J-TEC was incorporated into Teijin group and full-scale development of CGT&RM business took place.
- In Aug. '23, Teijin CDMO business was spun off into a separate company, and "TEIJIN REGENET" was launched.

What We Have

TEIJIN
TEIJIN REGENET CO., LTD.

Kashiwa-no-ha Facility (Chiba)
Feb.2024-
Facility area : **800** m²
4 suites

TEIJIN
TEIJIN REGENET CO., LTD.

Iwakuni Factory (Yamaguchi)
Jul.2024-
Facility area : **2,400** m²
10 suites(max)

J-TEC

J-TEC（Aichi）
In operation
Facility area : **5,500** m²

- Unique facilities that meet the needs of modalities and development stages (Chiba, Yamaguchi, Aichi)
- Seamless transfer from R&D to commercial is possible by sharing technology and know-how, exchanging personnel, etc.

Whom We Know

- Establish Kashiwa-no-ha RM PF together with Mitsui Fudosan and National Cancer Center
- Alliance with TFBS, Taiwan, and MediRidge regarding the supply of viral vector.
- Alliance with RESILIENCE, US, aim to realize innovative treatments through manufacturing

https://firm.or.jp/