

*CONFIDENTIAL*

# Company Presentation



June 2024

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# Company outline

|   |   |
|---|---|
| Name of the firm                                | Cuorips, Inc.   |
| Date of incorporation                           | March, 2017   |
| Accounting year-end                             | March   |
| C E O   | Takayuki Kusanagi   |
| Head office                                     | Chuou-ku Tokyo, Japan   |
| Research and manufacturing sites                | Osaka Lab<br>Suita City Osaka<br>Senri Research Center/Manufacturing Plant (CLiC-1)<br>Minoo City Osaka |
| Our business line                               | Development and commercialization of iPSC derived Cardiomyocyte Patches and CDMO business               |
| No of board of directors and corporate auditors | 8   |
| No. of employees                                | 59 (as of March 31, 2024)   |

## What is a human iPSC derived cardiomyocyte patch ?

Human iPSC derived cardiomyocyte patch is a product for regenerative therapy targeting severe heart failures which are currently not fully treatable with existing medical therapies. These patches are made using our technologies including those in-licensed from third parties on a large scale. Through joint research with Osaka University's Department of Future Medicine Division of Health Science (Dr. Sawa) and Kyoto University's iPSC Research Institute (Prof. Yamanaka), we seek to commercialize these products. By placing these patches onto the surface of the heart suffering from ischemia, abundant supply of cytokine is released from these patches into the myocardium, which is aimed to improve the blood circulation and hence to recover the heart function. In addition, cardiomyocyte contained in the patches will expand and contract simultaneously with the patients' heart muscle, which is aimed to assist the heart function.

We are conducting clinical trials in Japan, evaluating its safety and efficacy.



# Investment Summary

Global Front-runner in clinical development of iPSC-derived cardiomyocyte therapies aiming to connect R&D of Academia and Pharmaceutical Companies.

1

**Wide range of Network, Knowledge and Experience of Our CTO Dr. Sawa, who is a global authority in cardiovascular surgery**

Dr. Sawa created an appropriate clinical trial design in the development of iPSC derived cardiomyocyte patches. With a strong network of leading medical institutions and doctors, he has established research promotion system with renowned universities and research institutions in and outside of Japan, and has a wide variety of partner firms.

2

**We believe our clinical trial is at an advanced stage as compared to other clinical trials globally for development of iPSC-derived cardiomyocyte therapies**

All transplants necessary for clinical trials have been completed. Currently, preparing application for approval

3

**Manufacturing site for commercialization**

The company has a manufacturing site, available for manufacturing the iPSC-derived cardiomyocyte patches to initiate commercialization.

4

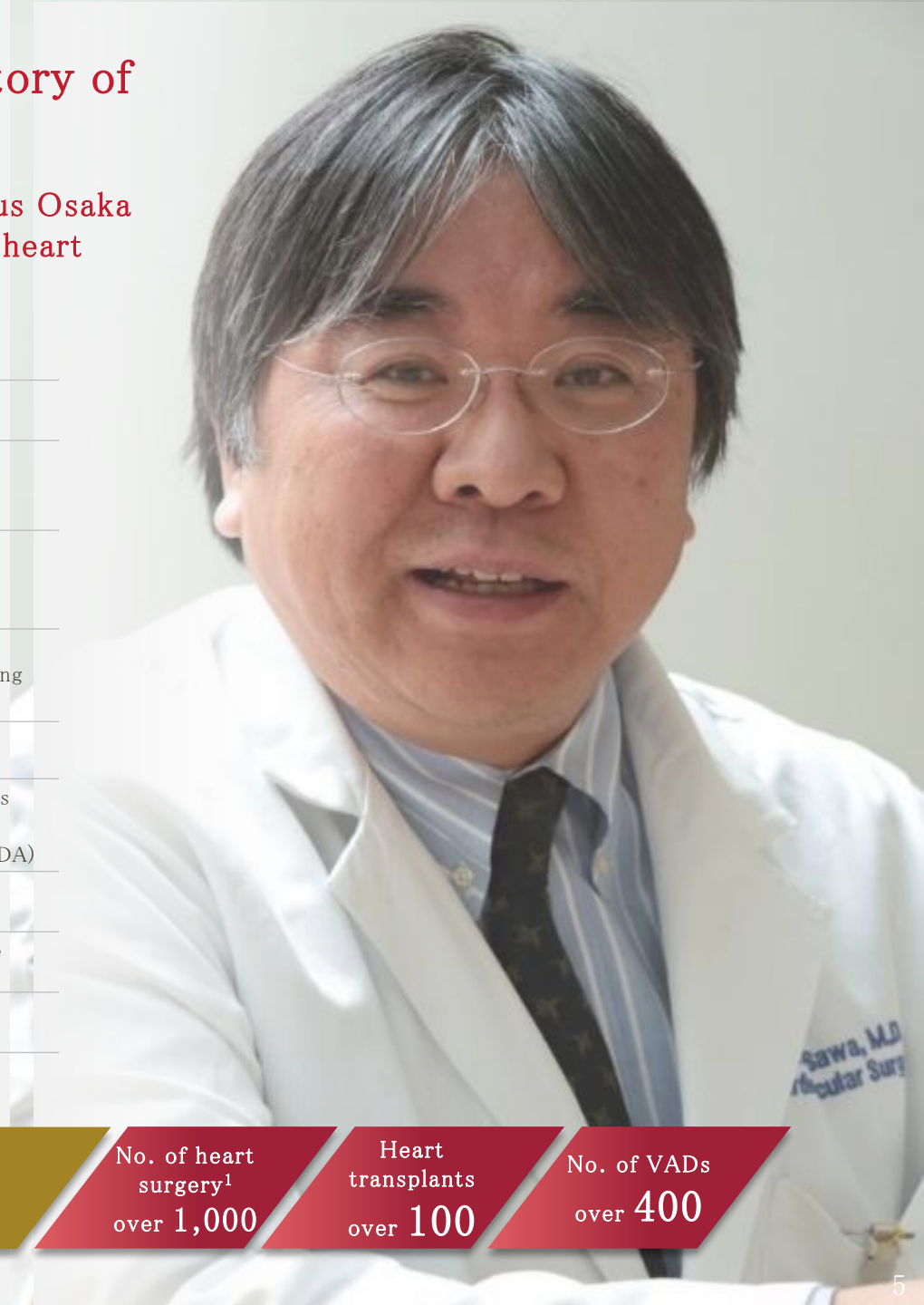
**Growth potential not limited to iPSC-derived cardiomyocyte patches**

Develops pipeline programs other than iPSC derived cardiomyocyte patches

# Achievements of Dr. Sawa and brief history of regenerative therapy

Under the leadership of our CTO Dr. Sawa (Prof. Emeritus Osaka University), we have made progress in the field of curing heart failures using iPSC.

|      |  |
|------|--|
| 2000 | Osaka University (Dr.Sawa's group) started research with Tokyo Women's University using patches for regenerative therapy of heart failures.  |
| 2006 | Dr. Yamanaka of Kyoto University succeeds in creating iPSC.  |
| 2007 | Dr. Sawa's group started research using patches from myoblasts. Dr. Yamanaka succeeded in creating human iPSC.   |
| 2008 | Osaka Univ. (Dr. Sawa's group) started joint research with Kyoto Univ. received iPSC from Kyoto Univ. and succeeded in differentiation from human iPSC to cardiomyocyte cells.   |
| 2012 | Dr. Sawa's group confirmed efficacy using large animals (pigs) and released research papers, and started clinical trials to severe heart failure patients using myoblast patches.  |
| 2013 | Our business received grant from AMED  |
| 2015 | We received clinical grade cell lines from Kyoto Univ., and started discussions with PMDA regarding manufacturing and non-clinical safety tests (※Terumo received approval for myoblast heart sheets (Terumo's product) from the PMDA) |
| 2016 | We created master cell bank for clinical grade iPSC  |
| 2017 | We started clinical research of iPSC derived cardiomyocyte patches to severe heart failures  |
| 2019 | We filed an application of investigator led clinical trials using iPSC derived cardiomyocyte patches   |
| 2020 | We started the above trials to the first patient   |



Aiming to save patients through combination of best science and practice

No. of heart surgery<sup>1</sup>  
over 1,000

Heart transplants  
over 100

No. of VADs  
over 400

1. Based on Dr.Sawa's own records

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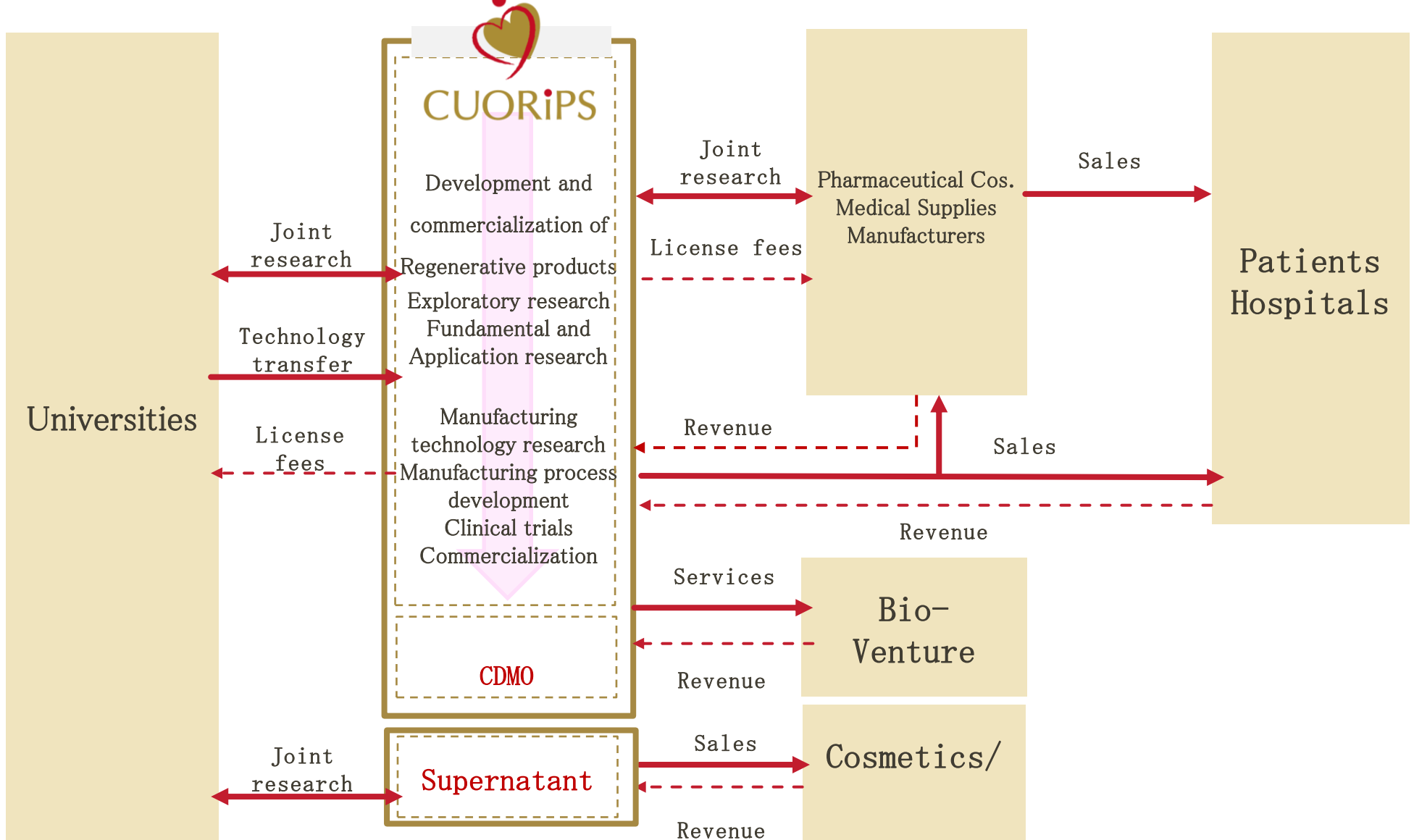
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# Business Model

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# Our business model

We aim to establish the following relationship with academia and pharmaceutical companies. The following is an image of the business diagram.





# Illustration of our planned profit profile model

While reducing downside risks with our businesses such as CDMO, we aim for a rapid growth from the launch of innovative new products.

\*For illustrative purpose only. Graphs and descriptions below do not represent any financial information of the Company

## Proprietary research model



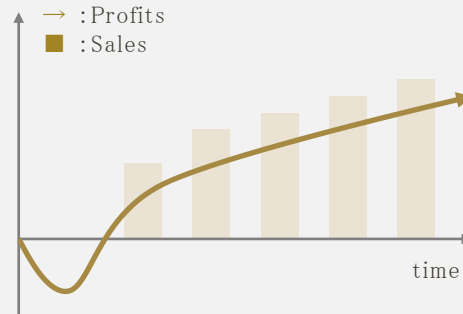
⊙ Huge growth after government approval

△ Difficult to achieve break-even early



High degree of business risk

## Joint research model

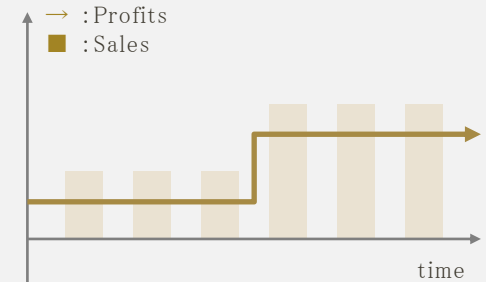


⊙ Break-even could be achieved early

△ Upside may be limited



## + CDMO model+Supernatant



⊙ Stable income

△ Upside limited






By combining the two profit profile  
We aim to realize stable cashflow early

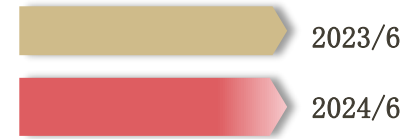
**Cuorips' hybrid model**

# Our business portfolio

Diverse set of business, in addition to our iPSC cardiomyocyte patches

| Business       | Category   | Brief Summary  |
|----------------|--|--|
| Cell Therapies | Domestic iPSC<br>Cardiomyocyte<br>patches<br> | <ul style="list-style-type: none"> <li>• <b>Cardiomyocyte patches for severe heart failures</b></li> <li>• <b>Indication</b><br/>               &lt;ICM&gt; Ischemic Cardiomyopathy: Severe cardiomyopathy caused by a narrowing of the coronary arteries which supply blood to the heart<br/>               &lt;DCM&gt; Dilated Cardiomyopathy: heart muscle disease that causes the heart chambers (usually the left ventricles) to become thin, stretch and grow larger. No cure except heart transplants             </li> </ul> |
|                | Overseas iPSC<br>Cardiomyocyte<br>patches  | <p><b>Same as above. Except for DCM</b></p>  |
|                | Catheters<br>                                 | <ul style="list-style-type: none"> <li>• <b>Providing cell therapies using catheter delivery to heart failure patients</b><br/>               (can be used by cardiovascular internal doctors)</li> <li>• <b>Indication</b><br/>               Acute myocardial infarction, coronary occlusion, chronic total occlusion</li> </ul>   |
| Others         | Regeneration<br>inducing factors   | <ul style="list-style-type: none"> <li>• <b>Angiogenesis, antifibrotic effect, anti-inflammatory effect caused by small-molecule drugs, as well as differentiation induction and tissue repair of myeloid stem cell</b></li> <li>• May be applicable to different organs (kidney, liver, lungs, etc.)</li> </ul>   |
| Supernatant    |   | <ul style="list-style-type: none"> <li>• <b>Cell processing facility with a built-in research lab having innovative technologies (CLiC-1)</b></li> <li>• Supernatant to cosmetic companies and clinics</li> </ul>  |
| CDMO           |  | <ul style="list-style-type: none"> <li>• CDMO to bio-ventures and consulting services to start-ups</li> </ul>  |

# Status of our pipeline



All of our pipeline have shown significant progress

|                      | Pipeline                      | Indication                                 | Exploratory research | Non-clinical | Clinical trials | Current status  | Partners                   |
|----------------------|-------------------------------|--|----------------------|--------------|-----------------|---|----------------------------|
| Cell Therapies       | iPS Cardio-myocyte patch      | PJ 1<br>ICM                                |                      |              |                 | Transplantation completed<br>Preparing for application      | Osaka U<br>Daiichi Sankyo  |
|                      |                               | PJ 2<br>DCM                                |                      |              |                 | Investigator led clinical trials underway at Osaka U        | Osaka U                    |
|                      |                               | PJ 3<br>Overseas ICM                       |                      |              |                 | Joint Research agreement imminent with major American Univ. | NA                         |
|                      | Catheters                     | PJ 4<br>AMI<br>CTO                         |                      |              |                 | Joint research with Asahi Intecc                            | Asahi Intecc               |
| Others               | Regeneration inducing factors | PJ 5<br>Liver Cirrhosis<br>NASH, ASO, etc. |                      |              |                 | Research underway   | Osaka U<br>Niigata U       |
| Supernatant Business | Secretome                     | PJ 6<br>Cosmetic Surgery, etc.             |                      |              |                 | Product development   | Cuorips Healthcare Science |

# CLiC-1 (Cuorips Labo-integrated Cell Processing Facility for Advanced Therapy-1st)

Manufacturing site combined with research lab. Construction through unique architecture and our unique concept.

Unlike most bio-start ups, we have our own manufacturing site, which we believe is one key source for our differentiation strategy.

## Our pipeline

We can manufacture our own pipeline at CLiC-1

We are considering other business using this facility



CLiC-1



## CDMO operation

We can provide CDMO services to other Bio-start ups at CLiC-1



**We can provide one-stop service ranging from manufacturing process development, actual production and quality control of regenerative therapeutic products and other cell products. We will also provide CDMO and consulting services.**

# Cell therapies

## (iPSC Cardiomyocyte patches)

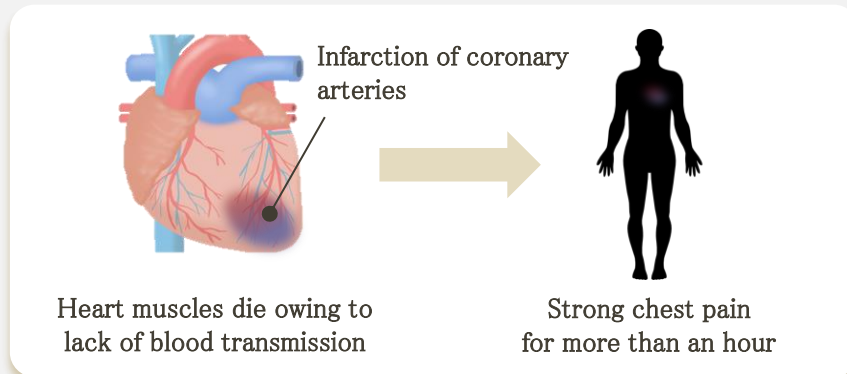
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# Indication of our products

Indication of our iPSC derived Cardiomyocyte patches: ICM (ischemic cardiomyopathy)  
DCM (dilated cardiomyopathy)

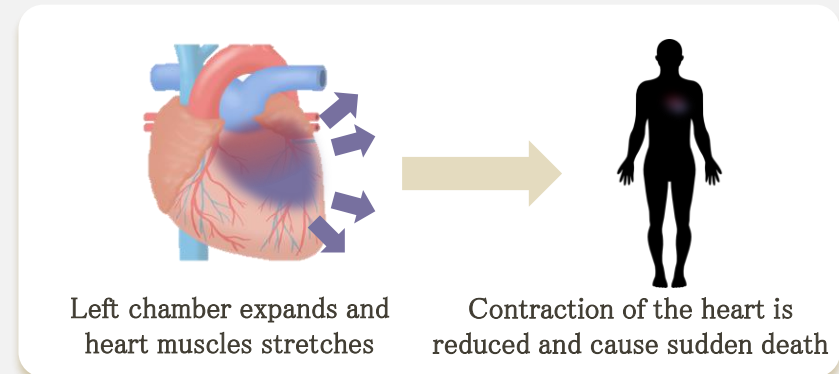
## Ischemic cardiomyopathy (ICM)

severe cardiomyopathy caused by a narrowing of the coronary arteries which supply blood to the heart



## Dilated cardiomyopathy (DCM)

heart muscle disease that causes the heart chambers (usually the left ventricles) to stretch, become thin and grow larger.



### Our 1<sup>st</sup> indication

Clinical trials

Last patient's operation completed

### Our 2<sup>nd</sup> indication

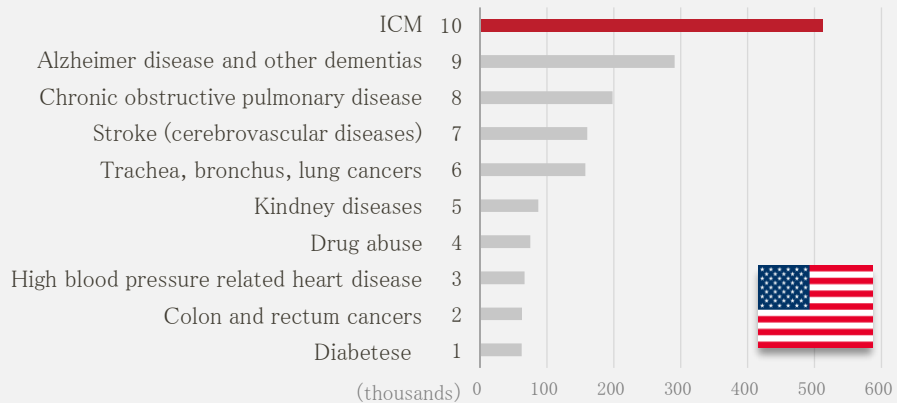
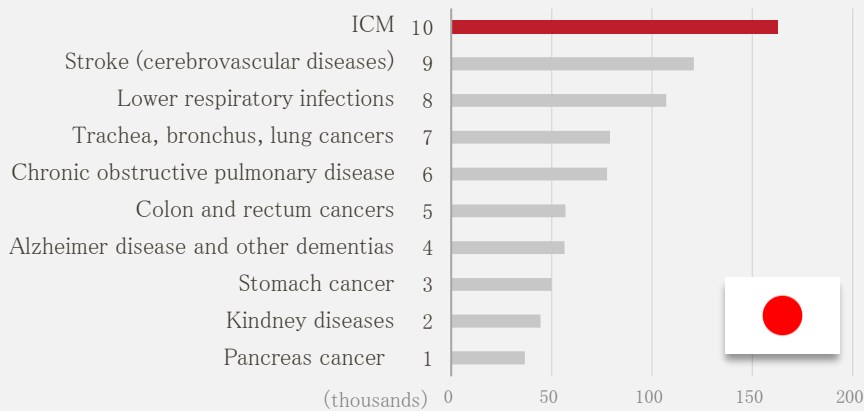
Clinical trials underway 2

transplants completed

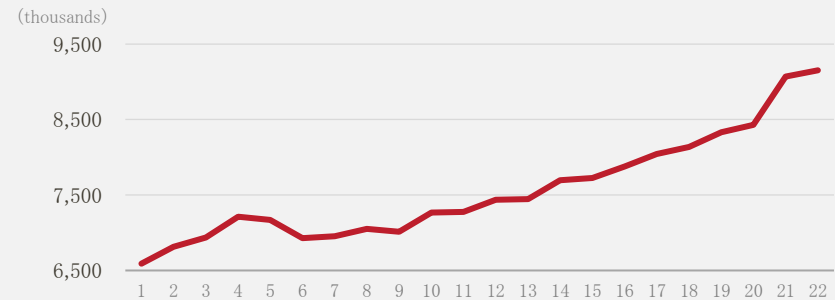
# Status quo of heart failures and estimate of number of patients

In both Japan and the U.S., ICM is the number one cause of death  
The number of deaths caused by ICM is increasing globally.

Cause of death ranking (2019)<sup>1</sup>



Number of worldwide deaths owing to ICM<sup>2</sup>



No. of heart failure patients and our target market<sup>3-5</sup>

| Country    | Patients | NYHA class III (25%) | NYHA class IV (5%) |
|------------|----------|----------------------|--------------------|
| Japan      | 1.3M     | 325,000              | 65,000             |
| U.S.A.     | 6M       | 1,500,000            | 300,000            |
| World wide | 26M      | <b>6,500,000</b>     | <b>1,300,000</b>   |

Heart failure severity classification (4 categories). Of all patients, 25% have class III disease and 5% have class IV disease. See page 18 for details.

1. WHO  
2. Calculated using number of patients per 100,000 released by Euromonitor and the number of population released by U.N.  
3. <https://world-heart-federation.org/resource/heart-failure-infographic/>

4. Global Public Health Burden of Heart Failure, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494150/>  
5. Leslie W. Miller, Left Ventricular Assist Devices Are Underutilized, Circulation. 2011;123:1552-1558, <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.110.958991>

# Expected merits of iPSC Cardiomyocyte patches

Two biggest merits are faster delivery to patients and medical cost reduction

## ① Donors are not needed

Our product will reduce the number of patients requiring artificial heart or heart transplants, thus reduce waiting period for heart transplants.

- Number of heart transplant requests: 842 as of end of May 2024
- Number of actual transplant in 2023: 115

(Source: Japan organ transplant network)

## ② Medical cost reduction

Our products will reduce deteriorating heart failure cases

(In the case of artificial heart) ※

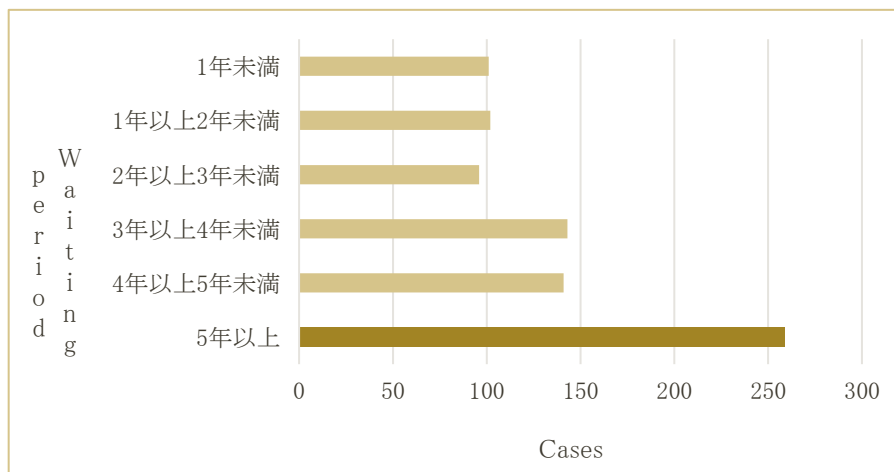
Initial cost 19 million yen, running cost (5.4million yen/annum)

Assuming 5 years total cost 46 million yen

(our estimate)

### Waiting period of heart transplants

| Waiting period  | No. of cases |
|-----------------|--------------|
| Less than 1 yr  | 101          |
| 1yr to 2 yrs    | 102          |
| 2yr to 3yrs     | 96           |
| 3yrs to 4yrs    | 143          |
| 4yrs to 5yrs    | 141          |
| More than 5 yrs | 259          |
| <b>Total</b>    | <b>842</b>   |



Source: Japan organ transplant network)

※ 厚生労働省「医療機器の保険適用について(平成23年4月) (<https://www.mhlw.go.jp/stf/shingi/2r985200000127vk-att/2r985200000127zm.pdf>)



# Expected Efficacy and Merits of our iPSC derived cardiomyocyte patches

The product can provide different merits to patients, hospitals, government, etc.

## ① Improvement of patients' QOL

Heart function weakened by myocardial infarction can be intermittently restored by LVADs<sup>1</sup> and heart transplants



In addition to this, the combined use of regenerative medicine with iPSC cell-derived cardiomyocyte sheets has the potential to enhance cardiac function and improves patients' QOL

## ② No need of heart donors

Through our therapies, we can avoid patients from heart transplants or LVADs. The treatment can save patients from lack of heart donors

- ✓ Registered heart transplants applicants as of June-end 2022<sup>2</sup>:921
- ✓ Number of heart transplants in 2021<sup>2</sup>:59 cases



Extremely long waiting time for available organs

## ③ Potential of reduction of cost

Potential of significant cost savings from our product

(vis-à-vis LVAD)<sup>3</sup>

- ✓ LVAD Cost 19million yen (about \$140,000)
- ✓ Maintenance fee 5.4 million yen/year (about \$40,000)



If we assume patient wearing LVAD for 5 years, total cost is 46 million yen (about \$340,000)

(\$1 = ¥135, as of May 12, 2023)

1. LVAD:Left Ventricular Assist Device A mechanical pump that is implanted in patients with severe heart failure

2. Japan organs transplant network

3. Ministry of Health, Labour and Welfare "Insurance Coverage of Medical Devices (April 2011)" (<https://www.mhlw.go.jp/stf/shingi/2r985200000127vk-att/2r985200000127zm.pdf>)

# Example of the World's first implant of iPSC derived cardiomyocyte patches

After successful production of the above patch, in Jan. 2020, a research group led by our Sawa CTO has successfully transplanted to the 1<sup>st</sup> clinical trial patient.

## Osaka University conducts world's first heart operation using iPSC regenerative therapy in the cardiovascular area.

Group led by Prof. Sawa of Osaka Univ. announced the first transplant of cardiomyocyte patches derived from iPSC cells on the 27<sup>th</sup> to a patient with severe heart failure. **The operation was conducted as Investigator-led clinical trials, and the results thus far have been quite good. The group will transplant to total of 10 patients within 3 years and will conduct research regarding its safety and efficacy.** Regenerative therapy using iPSC cells have already begun in the area of eye but the first in a vital organ such as the heart which is critical in saving life of a human being. Everybody is keen on its efficacy.

Investigator led clinical trials have begun in Dec. 2019, and the first operation was conducted in January at Osaka University Hospital to severe heart failure patient. No further details have been released.

Kyoto University created the cardiomyocytes using its iPSC cell stock. These cardiomyocytes have been frozen and stored. The patch was created according to the date of the operation, by defrosting the cells and forming them in a patch. During the operation, these patches were placed on to the damaged heart area. Its safety and efficacy will be observed during one year surveillance.

**At present, heart transplant is the only method for solving severe heart failure. However, such donor is extremely limited and there are many cases, where a patient cannot be operated.** Dr. Sawa expects that this product will turn into a competitive solution which will save so many lives. **If everything goes accordingly, a start-up venture Cuorips (Tokyo Chuo-ku) will commercialize this product.**

*From Nikkei (2020/1/27)*



Source: Osaka Univ.



1. *Investigator-led clinical trials: Clinical trials conducted by the doctors as opposed to conventional clinical trials initiated by pharmaceutical firms. Such trials were approved owing to the 2008 revision of the Pharmaceutical Affairs Law*
2. *Pictures provided by Osaka University (Jan. 20, 2020)*

## Research paper on Efficacy of three clinical trials by Osaka University ※1

- Osaka University published research paper on the three clinical trials
- No side effects, and deterioration of heart function was not observed and other material adverse effect was not observed from the transplant

### Summary of the paper

- No side effect, deterioration of the heart function was not observed but rather improvement in heart function was found.
- Improvement in scalability of left ventricle and blood flow was observed in two out of three cases.
- Regarding immune response, antibody value was increased in all three cases after completion of immunosuppressant. Moreover, in the one case of weak heart function recovery, increase in antibody value was observed vis-à-vis HLA-DQ(※2) even before the transplant.
- Conclusion: no problems were found in safety. However, more trials are needed to find the relationship between efficacy and immune response.

### NYHA ※3

Improvement in NYHA category was observed one year after the transplant.

|                       | NYHA | Subjective symptoms  | Case 1 |       | Case 2 |       | Case 3 |       |
|-----------------------|------|--|--------|-------|--------|-------|--------|-------|
| Good<br>↑<br>↓<br>Bad | I    | No symptoms during ordinary activities                                   |        |       |        |       |        |       |
|                       | II   | Symptoms during ordinary activities such as climbing stairs, and slope   |        |       |        |       |        |       |
|                       | III  | Symptoms observed during light activities such as walking on a flat road |        |       |        |       |        |       |
|                       | IV   | Heart failure symptoms observed during lying down or resting             |        |       |        |       |        |       |
|                       |      |  | Pre    | 1year | Pre    | 1year | Pre    | 1year |

※1 <https://www.frontiersin.org/articles/10.3389/fcvm.2023.1182209/full>

※2 Antibody which recognizes non-own cells and vitalizes immune system

※3 NYHA: New York Heart Association

# Addressable patient categories and comparison with other currently available treatments

iPSC derived cardiomyocyte patches are designed to treat patients until the symptom worsens to a stage requiring heart transplants. Catheters with less intervention is designed to treat a wider range of patients.

| NYHA<br>(New York Heart Association)<br>Category <sup>1</sup> |                         | I  | II   | III   | IV  |
|---|-------------------------|--|--|---|---|
|   |                         | No symptoms during ordinary activities<br>(35%) <sup>3</sup> | Symptoms observed during ordinary activities such as climbing stairs or slope.<br>(35%) <sup>3</sup> | Symptoms observed during normal walking (flat roads)<br>(III A:15%, III B:10%) <sup>3</sup> | Symptoms of heart failure and heartache observed while resting<br>(5%) <sup>3</sup> |
| No. of patients <sup>2</sup>                                  | World wide : 26,000,000 |  |  | 6,500,000 (III B : 2,600,000)   | 1,300,000   |
|   | U.S.A. : 6,000,000      |  |  | 1,500,000 (III B : 600,000)   | 300,000   |
|   | Japan : 1,300,000       |  |  | 325,000 (III B : 130,000)   | 65,000  |



Source

1. TOA EIYO 「Cardiology Terminology Handbook NYHA Classification」  
(<https://med.toaeiyo.co.jp/contents/cardio-terms/test-exam-diagnosis/4-16.html>)
2. Global Public Health Burden of Heart Failure, 2017, 3(1) :7-11  
(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494150/>)
3. Leslie W. Miller, Left Ventricular Assist Devices Are Underutilized, Circulation. 2011;123:1552-1558,  
(<https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.110.958991>)



Research focus

# Potential advantages of iPSC derived cardiomyocyte patches

Significant difference in lead time for cultivation and processing is possible.  
 Potential mass production could reduce costs.

## iPSC derived cardiomyocyte patches



Our plant

Patch production

Patches can be delivered  
 Under normal temperature  
 on a timely basis



Hospitals

Patch transplant

Significant potential reduction  
 in lead time of cultivation  
 and processing is possible

Less invasive owing to iPS cells

No additional facilities necessary at each hospital

## Autologous cells



Cells obtained  
 from each patient

Myoblast cells obtained from each patient  
 High degree of invasiveness

Cultivation necessary



Cultivation Plant

Cultivation

Must collect myoblast cells from the patient before operation.  
 Must cultivate the cells at each hospital for 3 months.  
 Difficult for emergency operation.



Hospitals

Process into patches



Hospitals

Transplant of patches

Each hospital must have CPC.  
 Number of hospitals limited

# Benefits of iPSC cardiomyocyte patches

Feasibility of treatments could be improved compared to the existing myocardial therapy using autologous myoblast cells.

|   | Myoblast patches  | iPS derived cardiomyocyte patches  |
|---|---|--|
| Invasiveness before transplant                    | <p><b>High</b></p> <p>Must collect myoblast cells from the patient</p>                              | <p><b>Nil</b></p> <p>No invasiveness since allogenic cells</p>   |
| Timely action                                     | <p><b>Difficult</b></p> <p>3 months necessary to cultivate the cells collected from the patient</p> | <p><b>Possible</b></p> <p>No cultivation necessary. Can deliver the patches under normal temperature on a timely basis</p> |
| Number of hospitals which can offer our treatment | <p><b>Limited</b></p> <p>Must have CPC</p>  | <p><b>Widely possible</b></p> <p>No special facility necessary</p>   |

Significant improvement in feasibility of treatment is possible

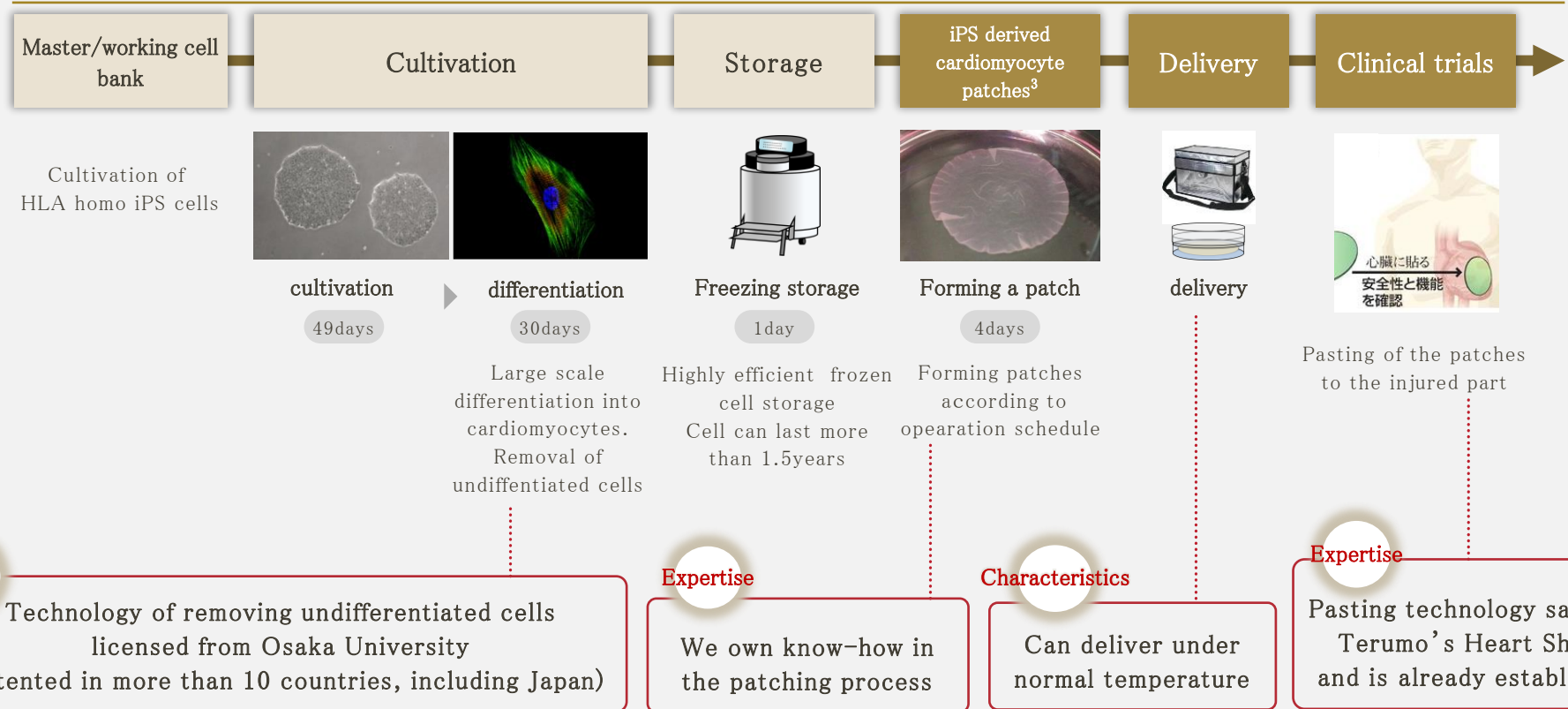


# Manufacturing process of iPSC derived cardiomyocyte patches

In regenerative cell therapy, manufacturing process is vital.

We have established a manufacturing process that could support potential commercialization including removal of undifferentiated cells and non-cardiomyocytes.

## Manufacturing process of iPS derived cardiomyocyte patches

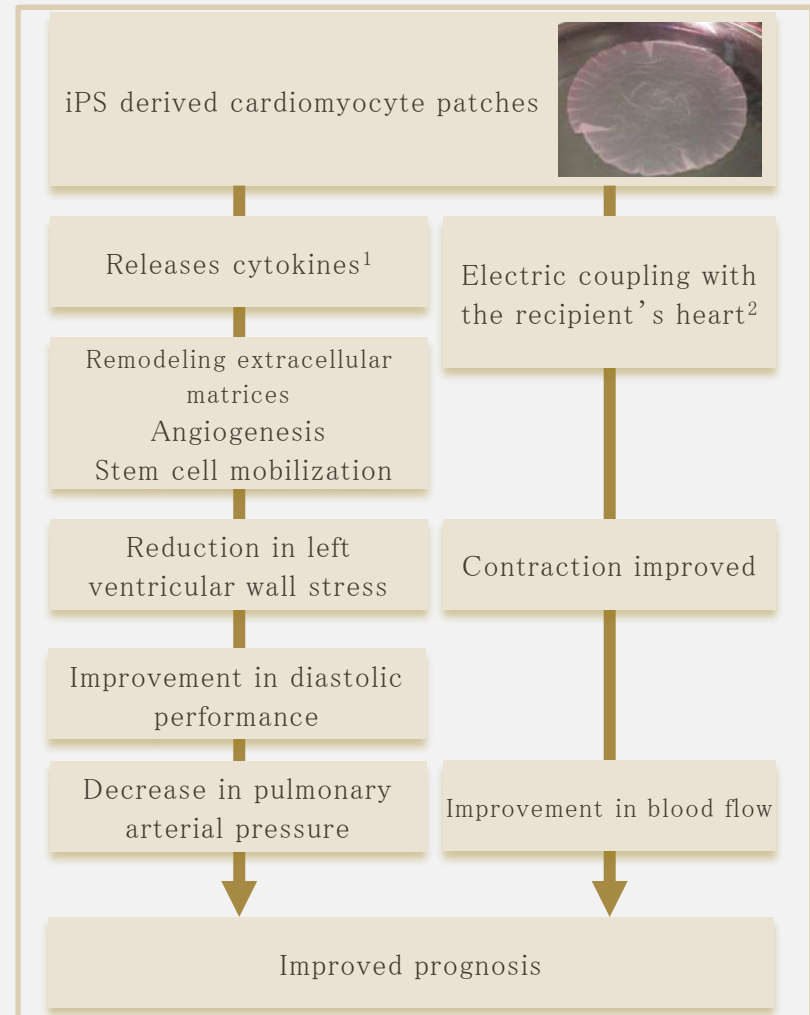
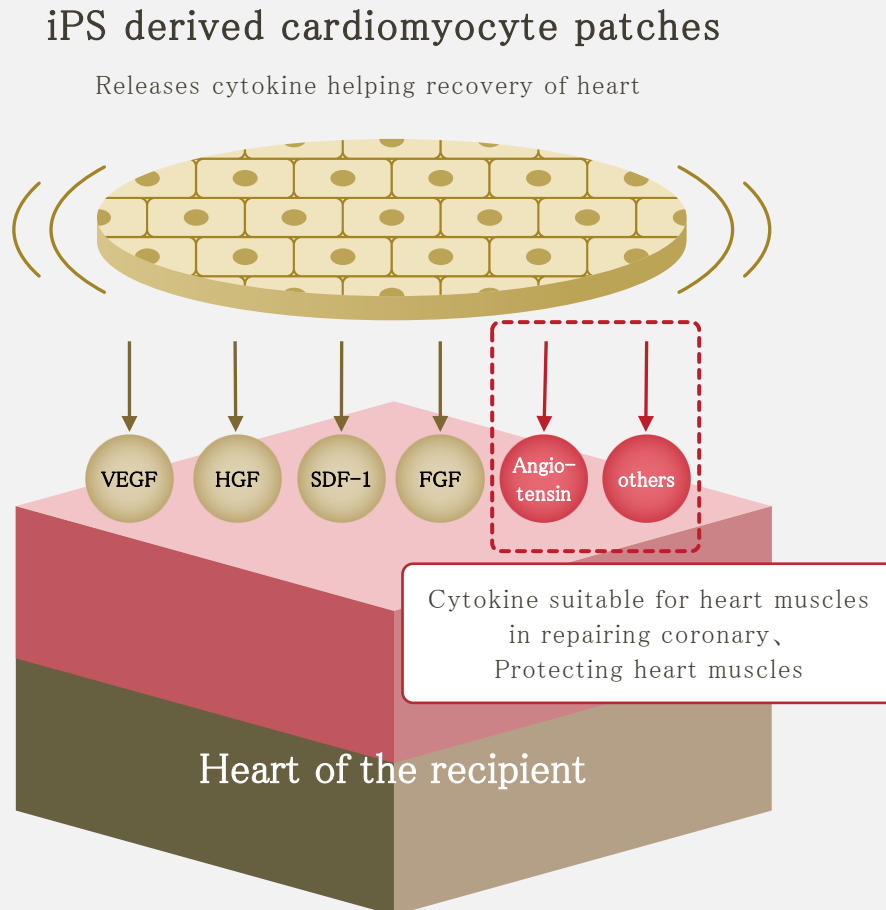


1. Undifferentiated cells means undifferentiated, undifferentiated iPS cells
2. Non-cardiomyocytes refers to cells other than the heart muscle that are derived from iPS cells. Non-cardiomyocytes in the process of cardiomyocyte differentiation are heart fibroblasts and vascular endothelial cells. Because undifferentiated iPS cells have tumorigenic properties, cardiomyocyte sheets derived from iPS cells carry the risk of becoming cancerous due to contamination by undifferentiated iPS cells. To avoid this, we eliminate non-cardiomyocytes by culturing them in a medium in which non-cardiomyocytes can not survive, taking advantage of the difference in metabolism between non-cardiomyocytes and cardiomyocytes, including undifferentiated cells. In addition, it is a drug in which the toxin is cross-linked to an antibody against an antigen specific to the surface of undifferentiated cells, which reduces the risk of cancer by selectively killing undifferentiated cells
3. Cardiomyocyte sheets derived from iPS cells become other people's cells, so patients need to be given immunosuppressive drugs to keep the transplanted cells alive after transplantation. Immunosuppressants have side effects on kidney function and the risk of infection, so in our company, the duration of immunosuppressant treatment is limited to the period during which the transplanted cells recover the heart tissue and function, and during that time the type and dose of immunosuppressants are tapered to reduce this risk

# Illustration of our preliminary analysis on potential mechanism of iPSC derived cardiomyocyte patches

We suspect that iPSC derived cardiomyocyte patches assist the recovery of the heart functions by secreting cytokine that better matches the heart muscles.

3



1. Cytokine: Small proteins produced and released from cells, activating a variety of biological processes in the recipient cells.
2. Recipient heart: Host animal or patient heart in the transplantation of iPSC-derived cardiomyocyte patches.
3. Transplantation of iPSC-Derived Cardiomyocyte Patches for Ischemic Cardiomyopathy (doi: <https://doi.org/10.1101/2021.12.27.21268295>)

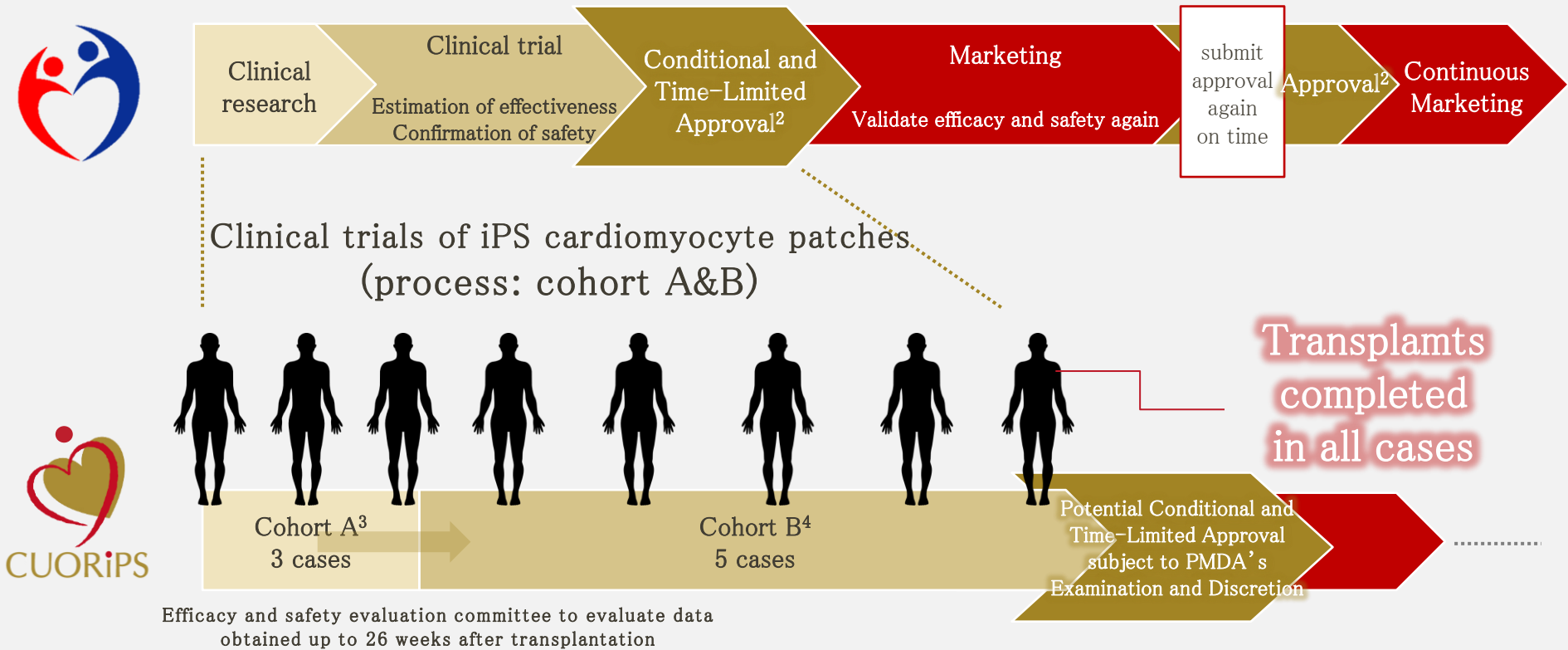


# Current status of Clinical trials of Cardiomyocyte patches for ICM

Clinical trial process for potential conditional and time-limited approval is as follows<sup>1</sup>:

All eight transplants originally planned for the clinical trial have been completed and ready for submitting application. (due during Oct.–December period)

## Conditional and Time-Limited Approval



1. Pursue early delivery to patients by utilizing the early approval system. Whether this approval or conditional and time-limited approval will be determined by the FDA at the time of approval
2. Pharmaceuticals and Medical Devices Agency: Provides health hazard relief for adverse drug reactions and infections caused by biological products, conducts approval reviews for the quality, efficacy, and safety of drugs and medical devices, and implements post-marketing safety measures
3. Cohort A: Phase to proceed with caution as this product is being transplanted into humans for the first time. Manufactured at the cell manufacturing facility of Osaka University Hospital
4. Cohort B: Phase that allows dose escalation. It is produced at the CLiC-C1 cell production facility in our company

# Comparison with our peers

We have made significant progress in allogenic cardiomyocyte patches vis-à-vis our peers.

|          |                | Cells                       | Autologous /Allogeneic | Delivery                            | Indication                         | Safety Tumorigenicity | Clinical Trials <sup>1</sup>   |
|----------|----------------|-----------------------------|------------------------|-------------------------------------|------------------------------------|-----------------------|--|
| Japan    | <b>Cuorips</b> | iPSC derived cardiomyocytes | Allogeneic cells       | Patches                             | ICM                                | ○                     | <b>All 8 cases transplanted</b> under the investigator led clinical trials |
|          | Company A      | ditto                       | Allogeneic cells       | Direct injection into heart muscles | Severe heart failure from ischemia | Unknown               | First case completed   |
|          | Company B      | ditto                       | Allogeneic cells       | Patches (Absorbs into the body )    | Chronic heart failure              | Unknown               | Pre-clinical/Pre-IND   |
|          | Company C      | Autologous myoblast         | Autologous cells       | Patches                             | Chronic heart failure              | ○                     | Approved by PMDA on a conditional basis                                    |
| Overseas | Company D      | iPSC derived cardiomyocytes | Allogeneic cells       | Patches                             | ICM                                | Unknown               | Pre-clinical   |
|          | Company E      | iPSC cells                  | Allogeneic cells       | Patches (absorbs into the body)     | Chronic heart failure              | Unknown               | Pre-clinical   |

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# Cell therapies (Catheter)

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# Catheter: Joint Research and Development with Asahi Intecc

Development program in the area of PCI (through the percutaneous coronary intervention) geared towards not only severe but also mild heart failure patients<sup>1</sup>.



Expertise in large scale cultivation and differentiation of iPS cells

Development of iPS derived cells suitable of catheter delivery

Joint Dev. Contract

Development of special catheters using sophisticated material processing technology

Establishment of wide spread New cell delivery methods

**Aiming to make huge contribution to add less invasive regenerative therapies to patients suffering from heart failures**

## New Catheter Delivery

iPS derived new cells through catheters



- New solutions to AMI<sup>※2</sup>、CTO<sup>※3</sup> patients (roughly 10 to 20% of 200 to 300K PCI patients may be applicable, the numbers are from Japanese Circulation Society)
- More involvement by cardiologists

Estimated no. of patients per year  
**20,000<sup>※4</sup>**

※1 In AMI, cells are transplanted to the site of rapid death due to oxygen and nutrient delinquency caused by the infarction, thereby potentially restoring the damaged tissue. As for CTO, it is expected that cardiac function can be restored by transplanting cells into the part of the heart muscle that has been lost due to obstruction and allowing it to be repaired

※2 AMI (Acute Myocardial Infraction) : Acute Myocardial Infarction

※3 CTO (Chronic Total Occlusion) :

※4 Company estimate based on the Japanese Circulation Society; JROAD (The Japanese Registry of all cardiac and vascular diseases)

# Other Pipeline

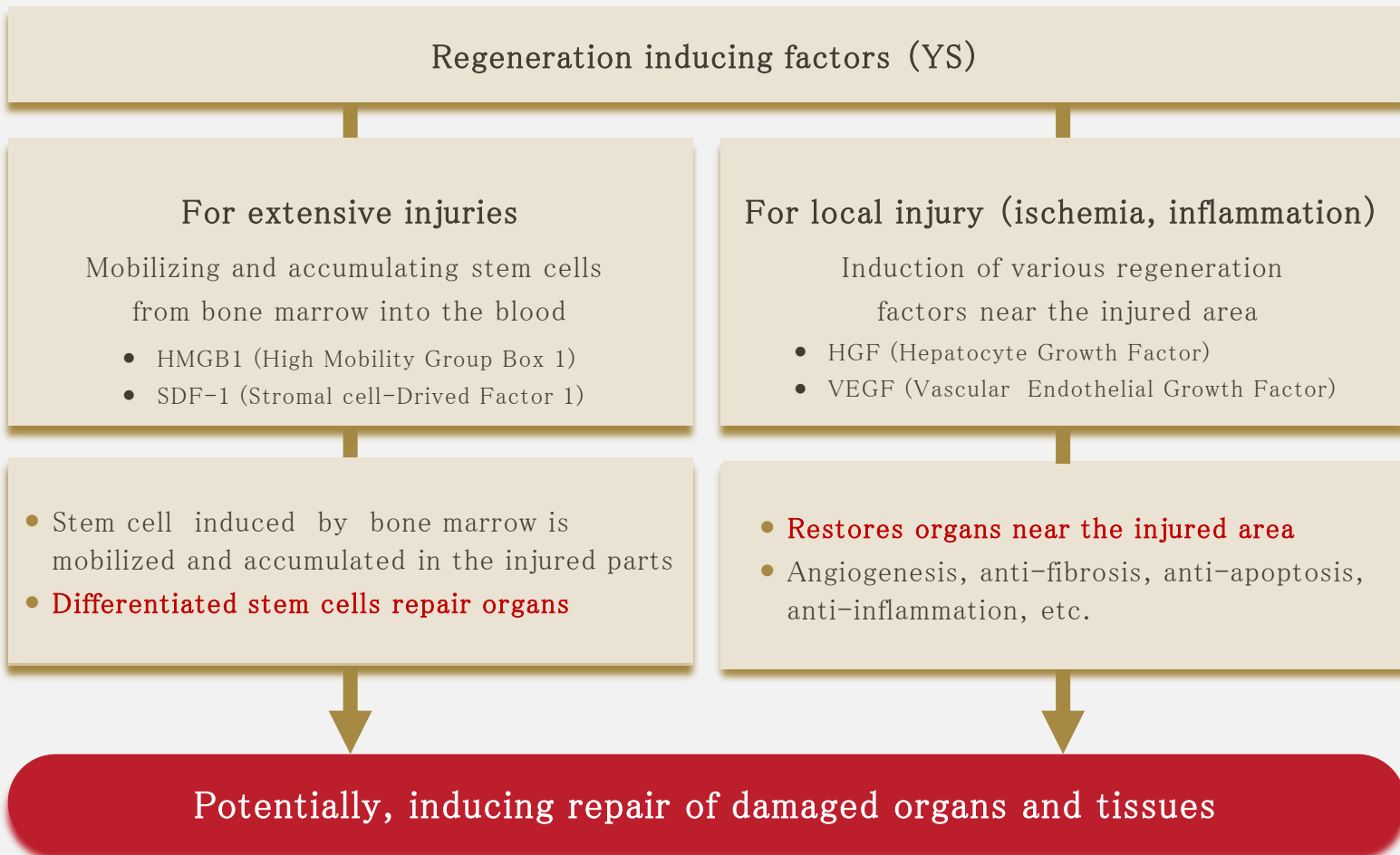
(Regeneration inducing factor)

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# Characteristics of Regeneration inducing factors (YS)<sup>1</sup>

## – illustration of two potential actions

YS has the potential to augment natural healing power which all humans originally possess. On that basis, We expect YS can induce regeneration of organs and tissues



1. Exploratory research is underway with Osaka University, and an agreement has been signed with Nagoya University to provide the drug. Preparing for multi-academia exploratory research and exploring development partners in parallel.

Source: [Lind Pharma, Inc.]

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# CDMO business

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# Our CDMO business model

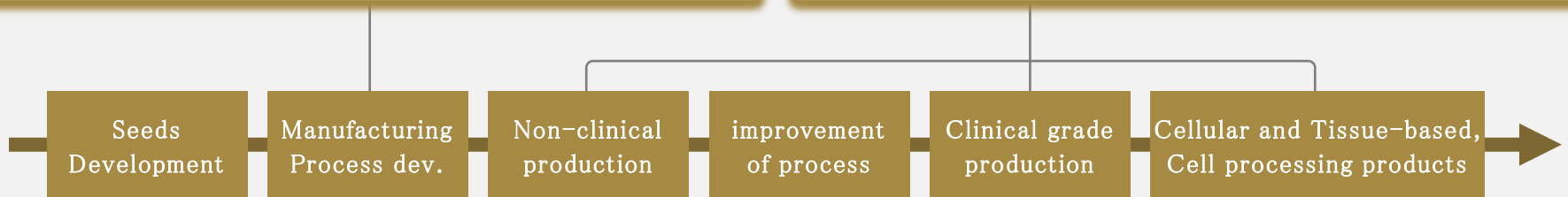
Our one stop service of providing product development service based on our experience of commercialization of Academia research and utilizing our sophisticated manufacturing sites  
 Effective use of our resources and improvement in capacity utilization

Strong technology development expertise as evidenced by our iPSC derived cardiomyocyte patches

- Large scale production of homo iPSC derived cardiomyocyte cells
- Patching forming, storage and delivery technology
- Technology in removal of undifferentiated iPSC cells

Manufacturing site with lab capabilities (CLiC-1) Filed for patents

- Single manufacturing site ranging from non-clinical and clinical products
- Huge efficiency resulting from shorter period of technology transfer
- Innovative and unique architecture for large scale production



- Production for regenerative products for our clients
- Consulting services for regenerative medicine
- Currently we have suspended seeking new business since we are filing an application to PMDA for our Cardiomyocyte patches





NEW

PJ 6

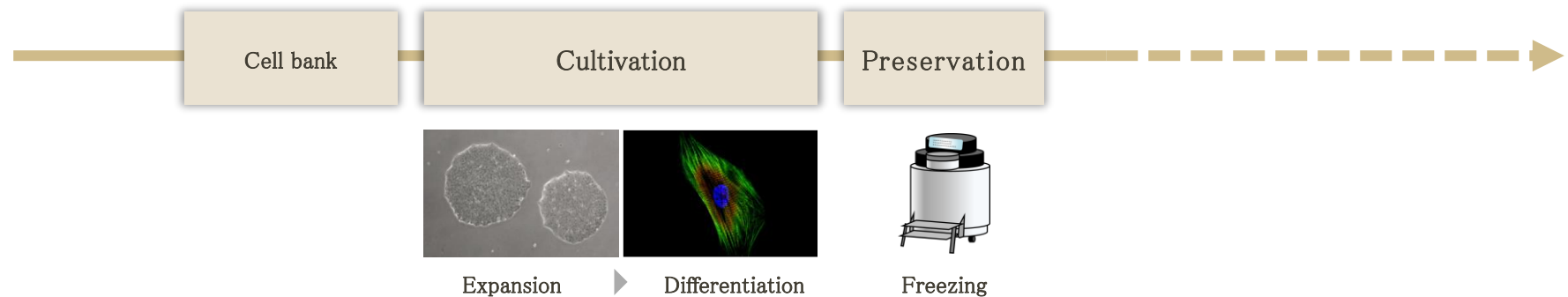
# Supernatant Business

## Summary of supernatant business

- Established in Dec., 2023, Cuorips Healthcare Science as our consolidated subsidiary
- Began utilizing supernatant derived from cardiomyocyte culture

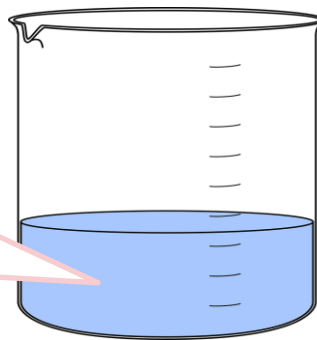
### Process of cell cultivation

Cell therapy business



Supernatant business

Includes many growth factors, Cytokines, and exosomes, etc.



Collection of culture medium

Removal of impurities

Increasing purities

Developing our original product to be used in clinics and raw materials for cosmetics, etc.

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# Growth strategy

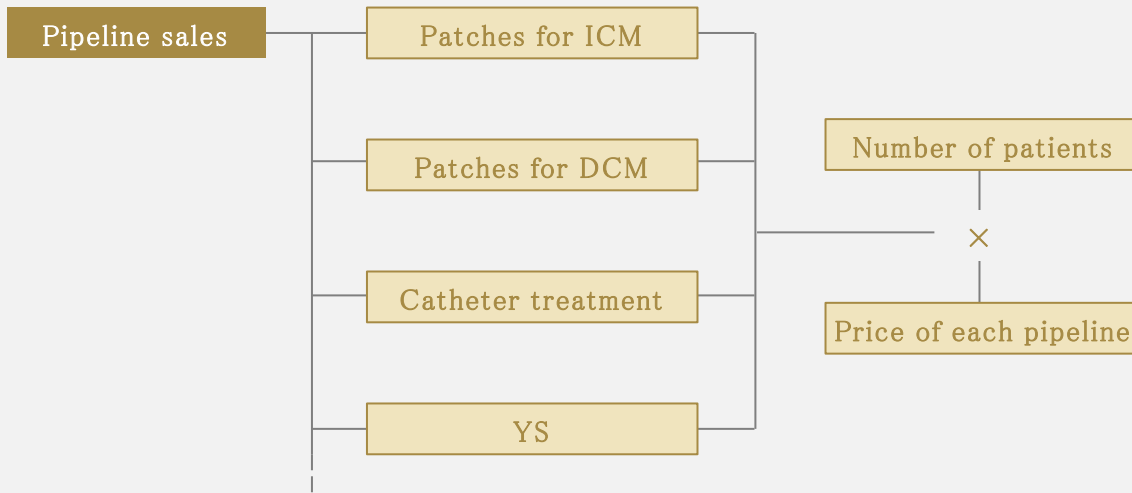
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# Assumptions of profits by each segment

Our profit profile is consisting of sales from each pipeline and CDMO operations

Pipeline sales are derived from multiplying expected price and expected number of patients

## Breakdown of pipeline sales



## Reference

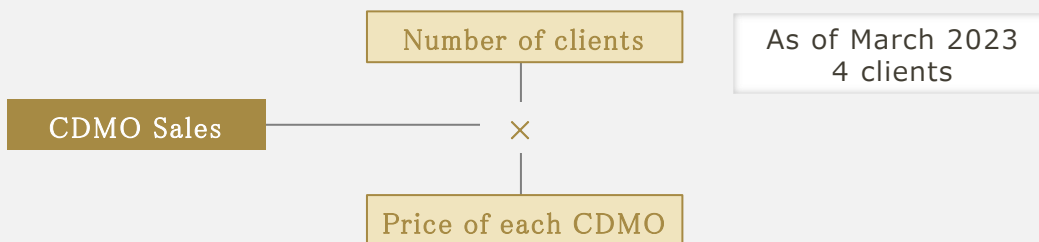
Number of target patients

Japan: 5,000<sup>1</sup>/US: 20,000<sup>2</sup> per year

Number of catheter patients

Japan: 20,000<sup>3</sup>/US: 100,000<sup>2</sup> per year

## Breakdown of CDMO business

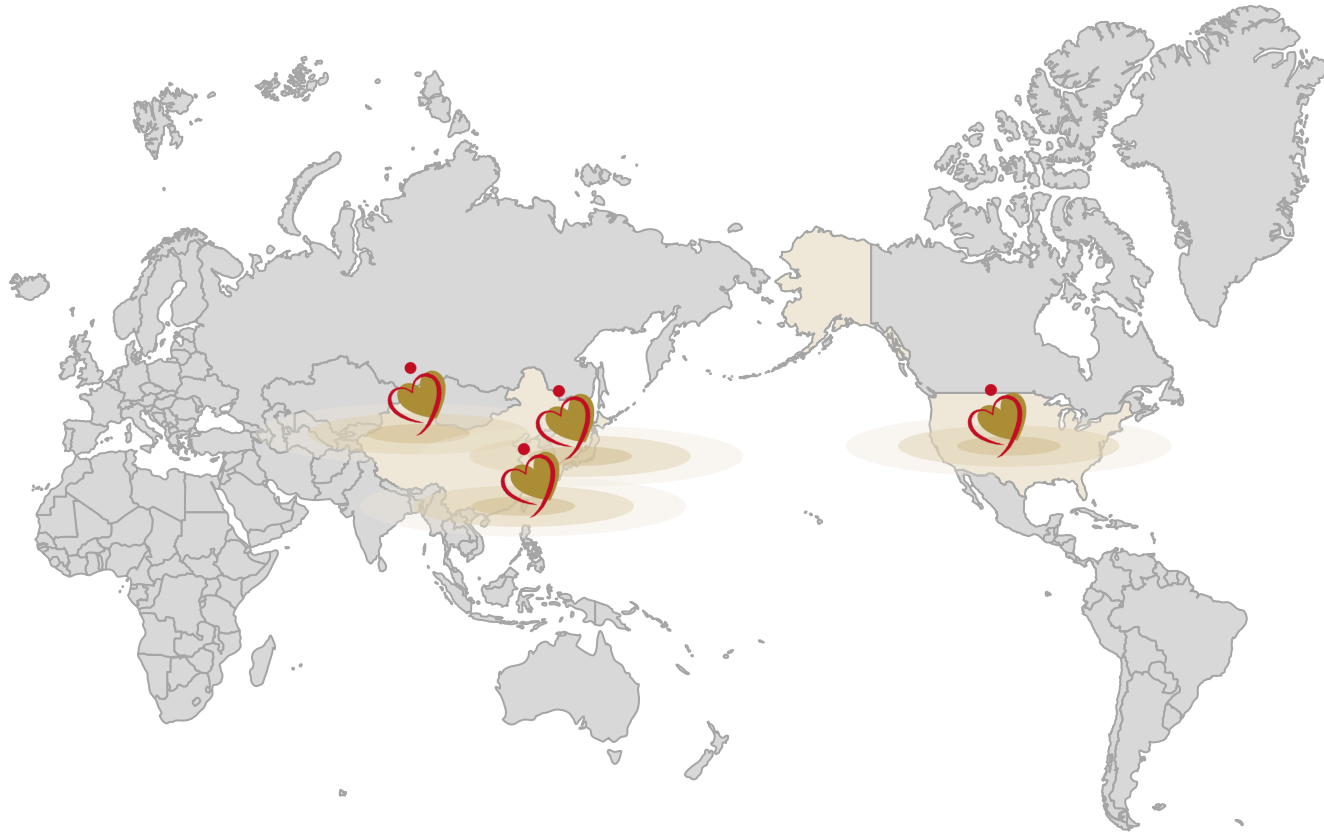


Source

1. According to the 2017 Patient Survey published by the Ministry of Health, Labour and Welfare, there are 70700 patients with ischemic heart disease (including 15000 hospitalized patients) and 9400 patients with old (chronic) myocardial infarction, for a total of approximately 80,000 patients receiving annual treatment. For the 15000 inpatients, analogizing to NYHA functional class grades III to IV, the ratio of grades III to IV in the NYHA functional class is 5:1, as described above. From this, we can infer that there are 12500 people in Grade III and 2500 in Grade IV. Since the ratio of grade III A to grade III B is 1.5:1, we estimate that the number of eligible patients (grade III B) for human iPS cell-derived cardiomyocyte sheets in Japan on an annual basis is 5000.
2. Calculated based on a 1:5 ratio of total patients between Japan and the United States
3. See page 26

## Overseas expansion plans

- U.S., China, Taiwan and the Asian markets to be one of our possible candidates
- Want to accelerate our overseas expansion once Japanese approval is concluded



# Our US operations

Currently, we have set up an office within “Japan Innovation Campus” which was established by METI at Silicon Valley

- METI wants to foster competitive Japanese start-ups to be able to compete in the overseas market and hence establish a successful venture eco-systems. METI has chosen us as one of strong candidates to be successful in the overseas markets



Source : METI

## Our major goal for FY 2025

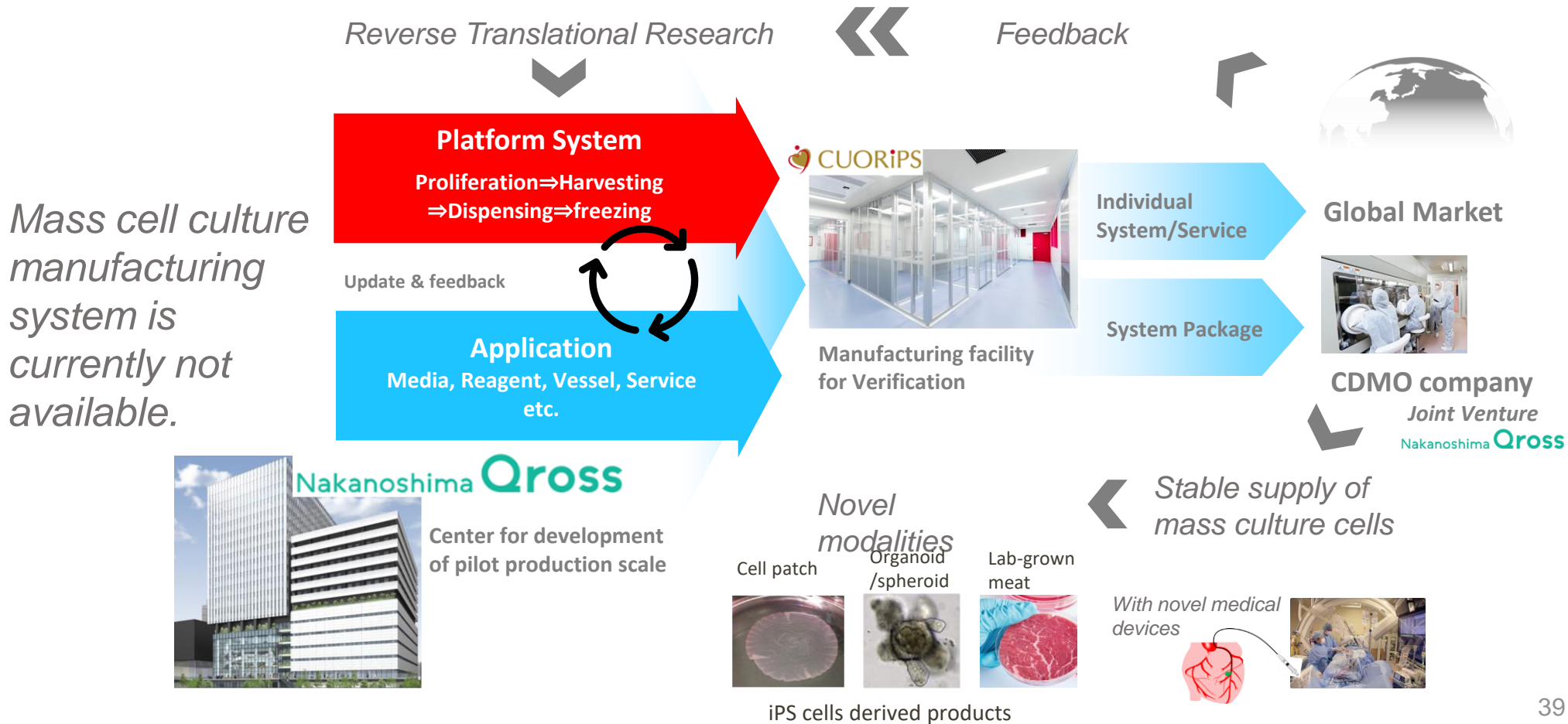
- Establishment of our US subsidiary
- Start a joint research program with U.S. institution

We have a goal to bring our products to the U.S. market  
Our U.S. subsidiary iReheart Inc. was established in June

# Joint research to promote large scale cell production system

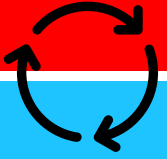
## Concept

### Value chain consortium for development of mass cell culture system



# Participating Companies

**Platform System**



**Application**



Novel Mass Cell Manufacturing Facility (WO2021/125042)



Auto cell culture system for adherent culture



Auto cell culture system for suspension culture



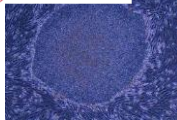
Auto dispenser



Be cool, Be alive.



Program Freezer



iPS Cell Bank System for clinical use



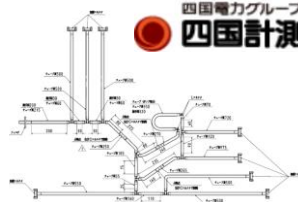
Unique method for Differentiation/Purification



Cryopreservation solution/technology



Cryovial Freezing bag



Single-use Container Feeding line Circulation line



MES-LIMS system for Manufacturing & QC/QA of Regenerative Medicine



# Image of our business segment growth



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# Appendix

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# Management Team

Strong management team consisting of science, medicine, pharmaceuticals, finance, economy, law and accounting

## Takayuki Kusanagi

CEO

- 1981 Joined Industrial Bank of Japan
- CIO of YMR Asset Mgt., Director of Management Planning, Entrust Corp., etc.
- 2020/4 Our Advisor
- 2020/8 Appointed as CEO

## Tadayuki Tanimura

COO

- 2007 Joined Asahi Chuo hospital
- Ministry of Health and Labor, WHO, Roche Diagnostics Inc. Healthcare Excellence Headquarters Dept. head etc.
- 2024/4 Became director and in June appointed as COO and a member of the board of directors

## Yoshiki Sawa

Founder / CTO

- Pioneer of regenerative therapy in the heart area
- Awarded Medal with Purple Ribbon by the Japanese Emperor
- 2021/8 Our CTO and Board Member

## Tadashi Sameshima

Board member

- 1983 Joined Terumo Corp.
- 2016 Executive officer of Heart sheet business
- 2020 Management Advisor, Terumo
- 2021 Technical advisor of Cuorips
- 2022 Our board member

## Kenichiro Yoshida

Board Member

- 1985 Nikko Securities
- Goldman Sachs Managing director, Ichigo Asset Management Vice CEO, etc.
- 2024/6 Board Member

## Norihiro Ashida

Internal Auditor

- 1977 Joined Industrial Bank of Japan
- Otsuka Holdings Managing Director CFO of Hekabio
- 2024/6 Internal Auditor

## Kotaro Yamamoto

External Auditor

- 1991 awarded New York Bar
- 2020 External Auditor of Cuorips

## Shinji Abe

External Auditor

- 2007 Awarded CPA
- Chief Representative of Abe Accounting Firm (Current)
- Chief Representative of Abe Shinji Tax Accountin (Current)
- 2020 External Auditor of Cuorips

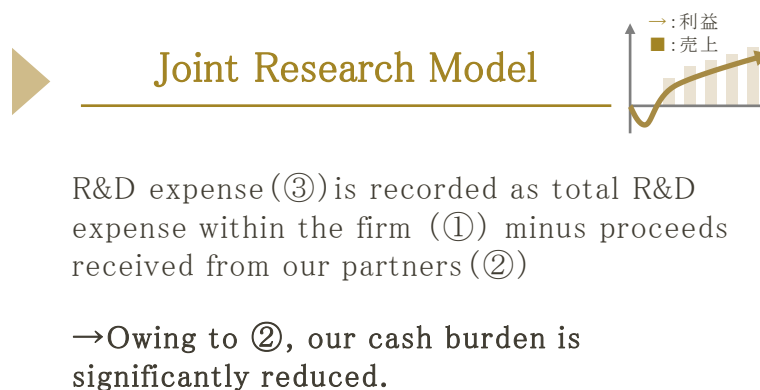
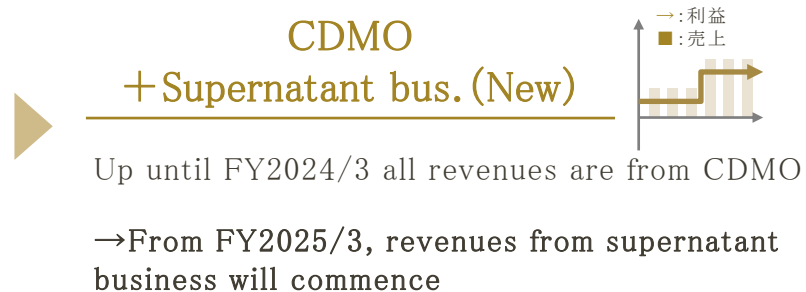
# Financial results

- Like most bio-tech firms, R&D expenses is heavy upfront.
- We want to reduce deficits by adding CDMO, Supernatant business and reduce R&D expense by entering into Joint research program

(Consolidated) Income Statement

(Unit: Thousand yen)

|   | FY2022/3 | FY2023/3       | FY2024/3       |
|---|----------|----------------|----------------|
| Sales                                   | 13,913   | <b>38,278</b>  | <b>23,102</b>  |
| COGS                                    | 3,260    | <b>17,266</b>  | <b>13,471</b>  |
| SGA ③+④                                 | 383,917  | <b>471,447</b> | <b>598,118</b> |
| (o/w Total R&D) ①                       | 655,546  | 648,463        | 788,853        |
| (o/w Received from Joint R&D partner) ② | △542,740 | △480,310       | △579,079       |
| Net R&D ③(=①-②)                         | 112,805  | <b>168,152</b> | <b>209,773</b> |
| Other SGA ④                             | 271,112  | <b>303,295</b> | <b>388,345</b> |
| Operating Loss (△)                      | △373,264 | △450,435       | △588,487       |
| Recurring Loss (△)                      | △373,140 | △450,418       | △627,930       |
| Net Loss (△)                            | △375,337 | △452,077       | △632,183       |



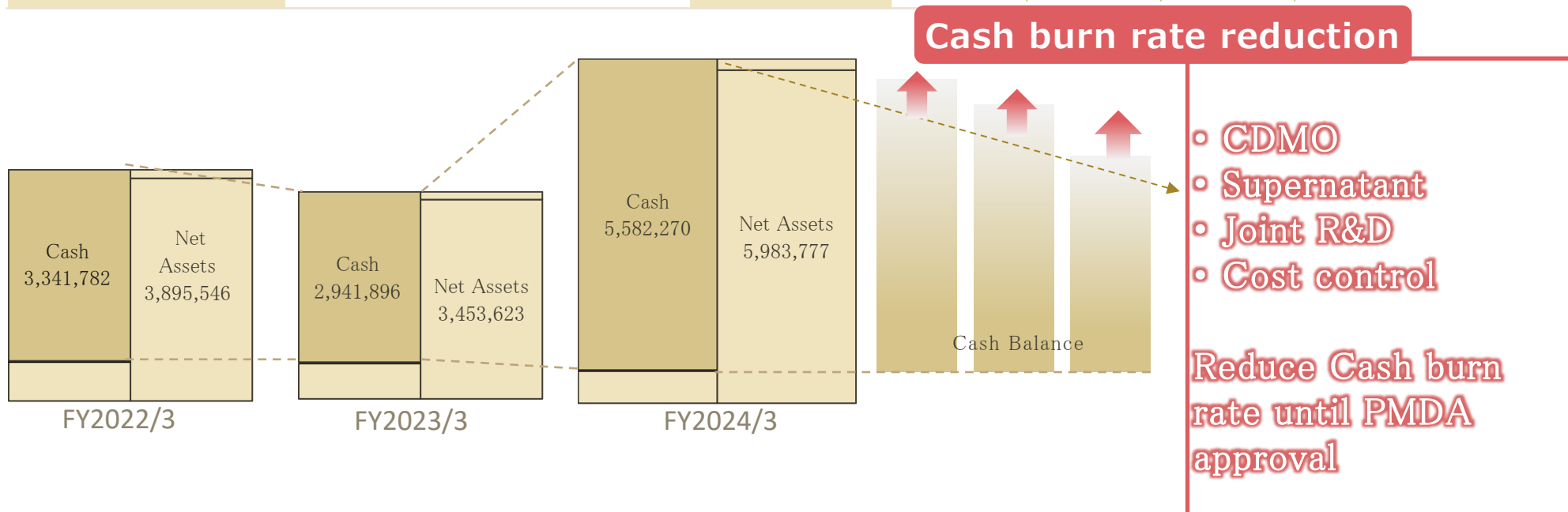
# Our financial condition

- Owing to IPO in June 2023, our cash position and net worth increased significantly
- FY2024/3 Cash/Total Assets 90.3% Total Capital/Total Assets 96.6%

## Consolidated BS

(Unit:Thousand yen)

|                        | FY2022/3  | FY2023/3  | FY2024/3  |                             | 2022/3期   | 2023/3期   | 2024/3期   |
|------------------------|-----------|-----------|-----------|-----------------------------|-----------|-----------|-----------|
| Current Assets         | 3,367,090 | 2,977,402 | 5,612,137 | Current Liabilities         | 112,410   | 97,425    | 166,015   |
| (o/w, cash deposit) ※1 | 3,341,782 | 2,941,896 | 5,582,270 | Fixed Liabilities           | 36,949    | 36,369    | 34,945    |
| Fixed Assets           | 677,816   | 610,015   | 572,600   | Total Capital               | 3,895,546 | 3,453,623 | 5,983,777 |
| Total Assets           | 4,044,906 | 3,587,417 | 6,184,738 | Total Liabilities & Capital | 4,044,906 | 3,587,417 | 6,184,738 |



# Cashflow

## Consolidated Cashflow statement

(Unit:thousand yen)

|                                    | FY2022/3  | FY2023/3  | FY2024/3     |
|------------------------------------|-----------|-----------|--------------|
| Operating Cashflow                 | △220,762  | △401,612  | △451,060     |
| Cashflow from Investment           | △28,444   | △8,968    | △34,998      |
| Cashflow from financial activities | 48,541    | 10,694    | 3,125,418    |
| Increase in cash                   | △200,665  | △399,885  | ※1 2,640,373 |
| Outstanding amount as of FY end    | 3,341,782 | 2,941,896 | 5,582,270    |

## Usage of IPO proceeds

- Plan to use to increase our pipeline
- Capacity expansion planned to accomodate increasing business from CDMO, supernatant

| Pipeline     |                                | FY2024/3<br>Actual | FY2025/3 onwards | Usage                         |
|--------------|--------------------------------|--------------------|------------------|-------------------------------|
| iPSC patches | <b>PJ 2</b><br>DCM             | 20 M yen           | 450 M yen        | Clinical trials               |
| iPSC patches | <b>PJ 3</b><br>Overseas<br>ICM | 30M yen            | 600M yen         | Clinical trials               |
| Catheters    | <b>PJ 4</b><br>AMI<br>CTO      | 20 M yen           | 1540 M yen       | Pre and Clinical trials       |
| CAPEX        |                                | —                  | 300 M yen        | Expansion of laboratory, etc. |
| Total        |                                | 70 M yen           | 2890 M yen       |                               |

*These figures may change owing to our strategy changes.*