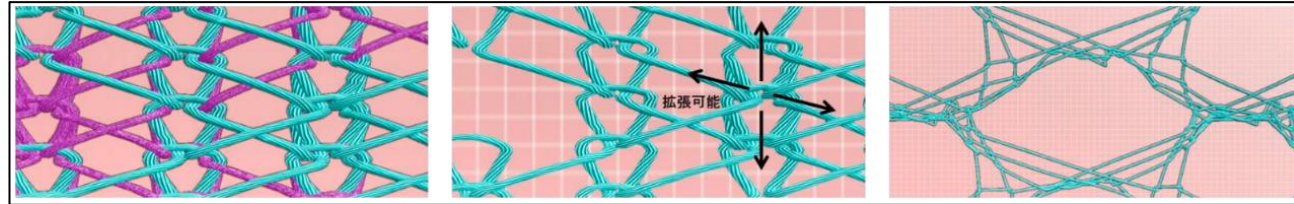
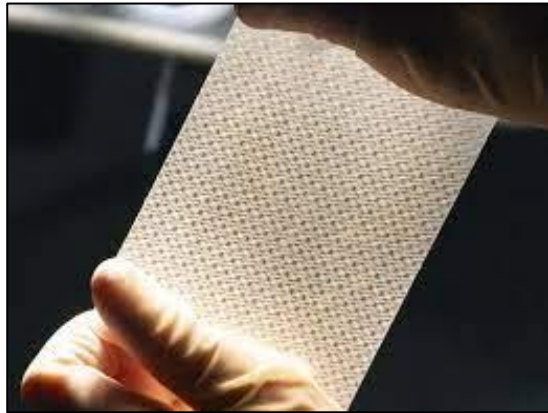


The road from development to approval of pediatric medical devices and future approach “SYNFOLIUM[®]” for congenital cardiac surgery



Osaka Medical and Pharmaceutical University
Department of Thoracic and Cardiovascular Surgery
Shintaro Nemoto

US-Japan HBD East Think Tank East Meeting 2023, Ariake, Tokyo
Session F-4, December 14, 2023

Unmet medical needs in pediatric cardiac surgery

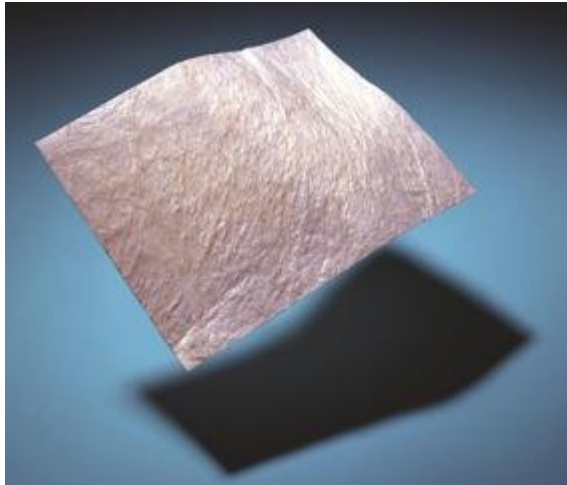
- Various kinds of xenograft and synthetic materials have been used in pediatric cardiac surgery. It is well known that **drawbacks** of the existing surgical materials have never been solved.
- Those are **material deterioration, calcification, fibro-intimal proliferation, shrinkage, and infection risk**, often resulting in hemodynamic disturbance.
- Those materials **can not be expandable** to be matched to the body size.

⇒ **Readmission, catheter intervention, and/or surgical replacement of the materials are often required.**



Currently available surgical products aiming for *in situ* tissue restoration

CorMatrix®



<https://cormatrix.com/>

- ✓ Decellularized xenograft
- ✓ Porcine intestinal submucosa
- ✓ Extracellular matrix
- ✓ patient's cell migrates for regeneration

CardioCel®



<https://www.lemaitre.com/products/cardio-cel-bioscaffold-patch>

- ✓ Decellularized xenograft (ADAPT)
- ✓ Bovine pericardium
- ✓ Extracellular matrix
- ✓ Patient's cell migrates for regeneration

High density fine fiber
non-woven fabric (**Xeltis**)



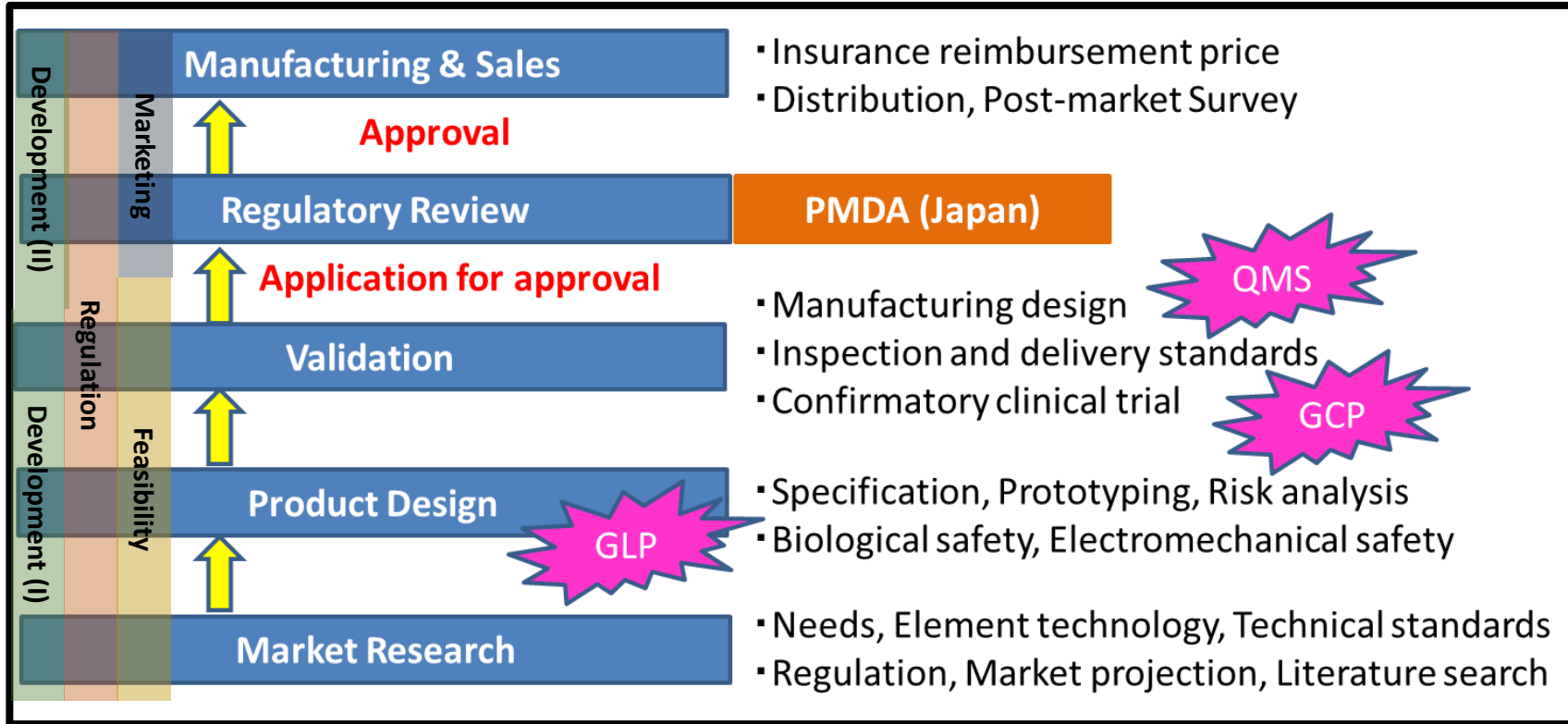
<https://xeltis.com/xeltis-initiates-first-ever-pivotal-trial-of-a-synthetic-restorative-pulmonary-heart-valve/>

- ✓ Absorbable super-molecular polymer
- ✓ Electrospinning molding
- ✓ Patient's cell migrates for regeneration

Still many barriers to overcome !

Complicated steps for medical device development

→ Everything Everywhere All at Once



Technology?
Intellectual Property?

Sterilization?
Production?
Logistics?

POC?
Regulation?
Reimbursement?

Sales? Distributor? Competitor?
Such, such, such!!!

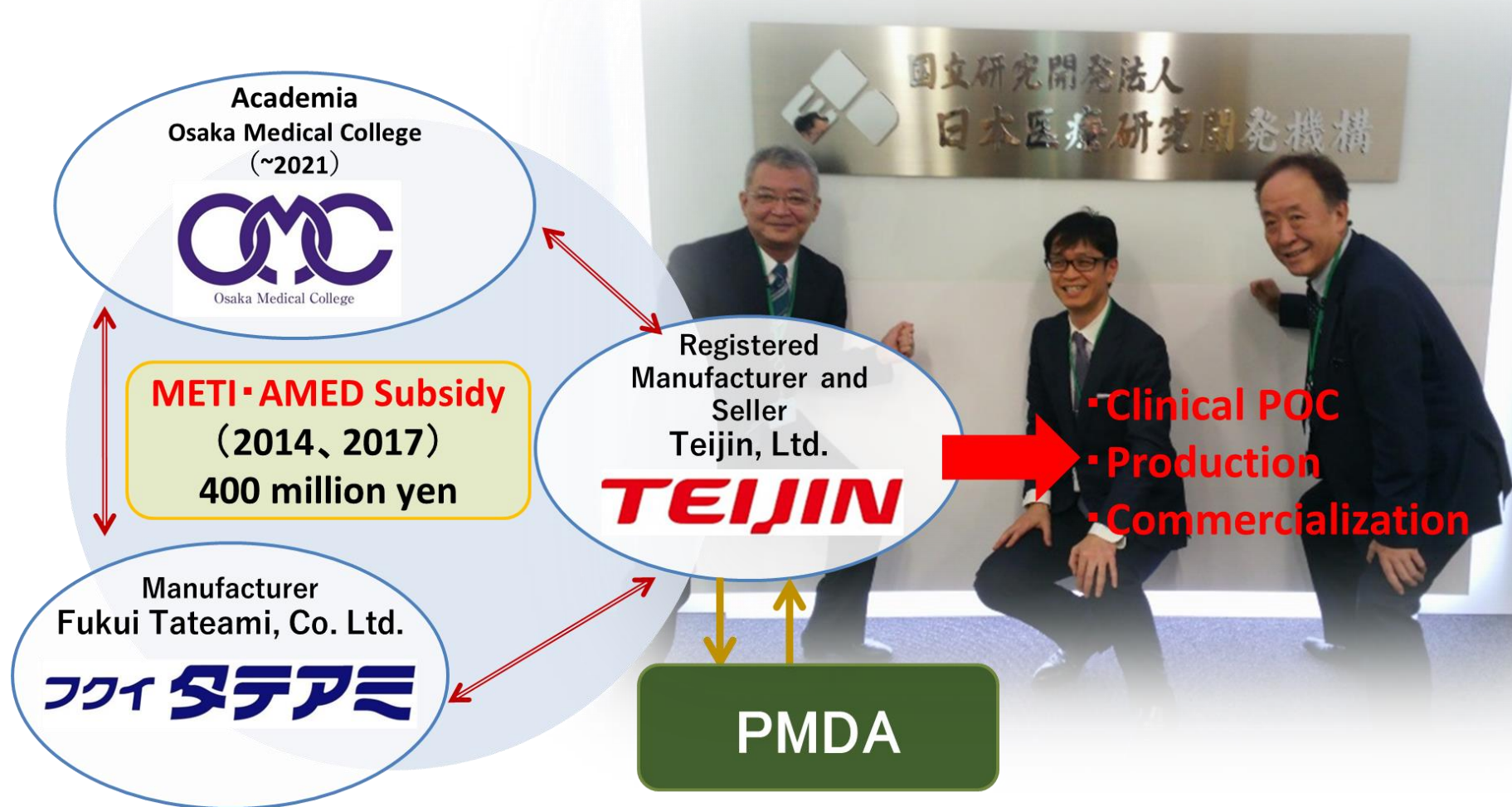
Strategic Objectives for Success

- Scientific and waste-free data-set in preclinical study sufficient for clinical trial
 - Minimum but valid clinical trial for regulatory approval
 - Market, business plan, and future product pipeline
- Sufficient reimbursement price for business continuity (predictability)

Start all at once by creating common ground by active industry-academia-regulatory authority collaboration!

Consortium formation first !

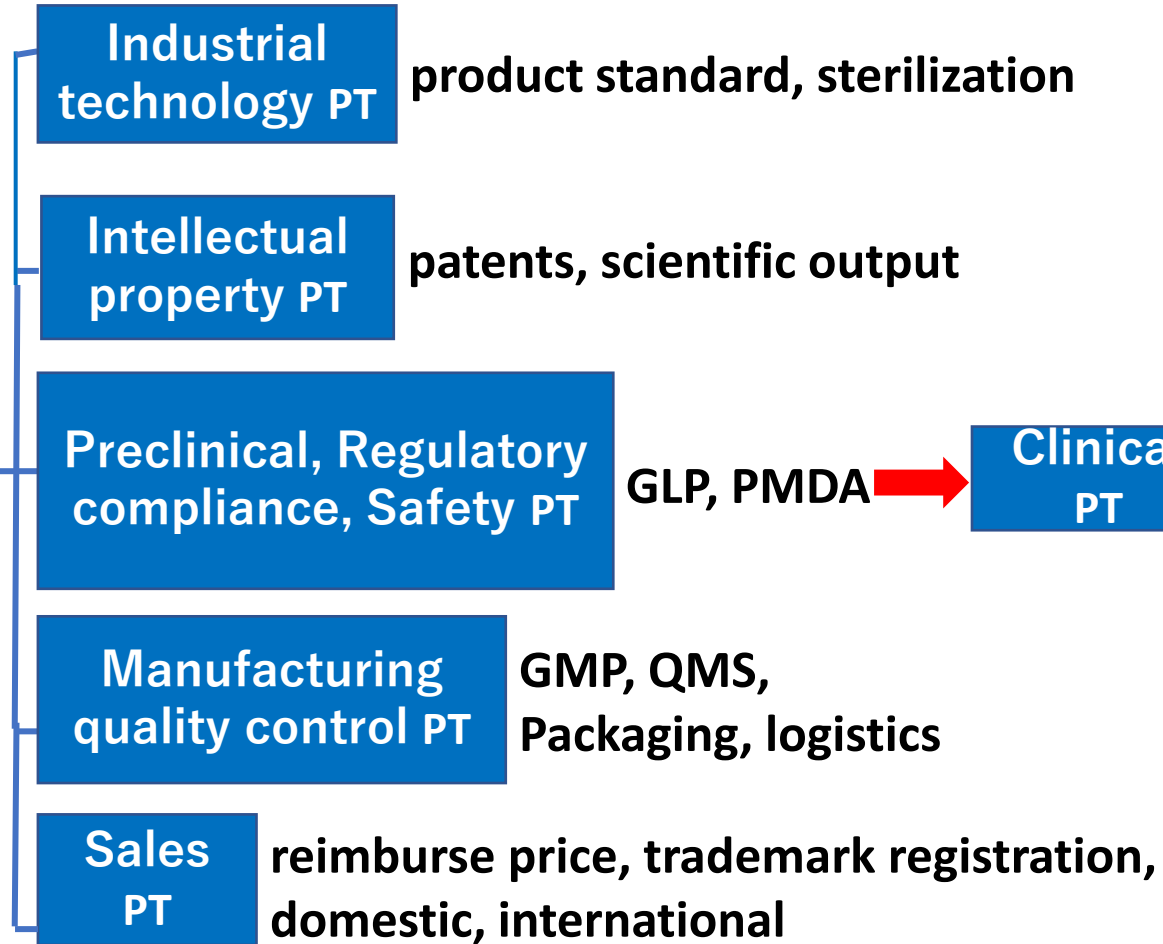
★ Subsidy and medical device specialist consultation provided from government



- Ministry of Economy, Trade and Industry (**METI**) & Japan Agency for Medical Research and Development (**AMED**)
- A dedicated program to **promote commercialization of medical devices by industrial - medical collaboration.**
- ¥ 400 million (\$ 3.03 million) subsidy for 6yrs & “goal-oriented” accompanying guidance toward successful commercialization

Consortium framework

goal-oriented simultaneous multistep approach



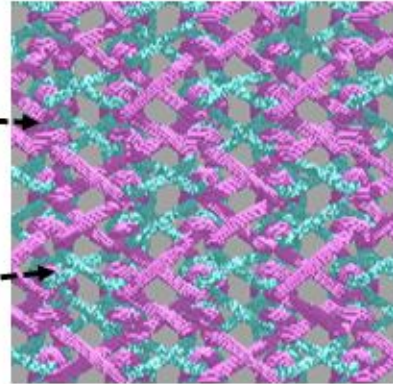
GCP, PMDA, academia society (JSPCCS)



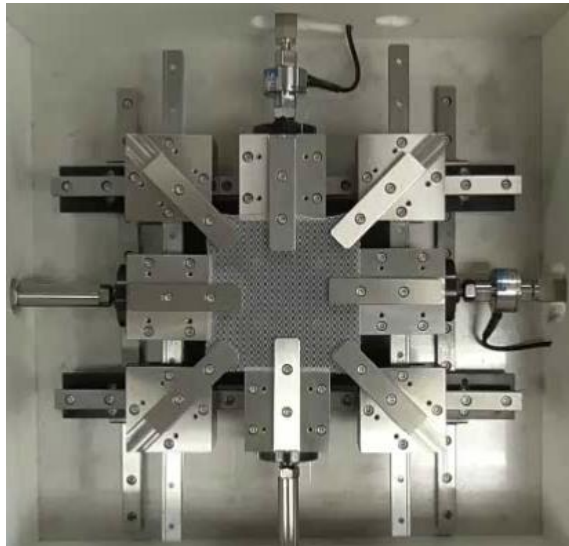
Concept & Component of OFT-G1 (code name)

Biodegradable (PLA)
yarn acts as hooks

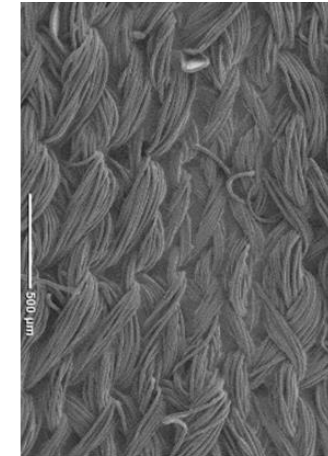
Non-biodegradable (PET)
yarn gives the extensible
and mechanical properties.



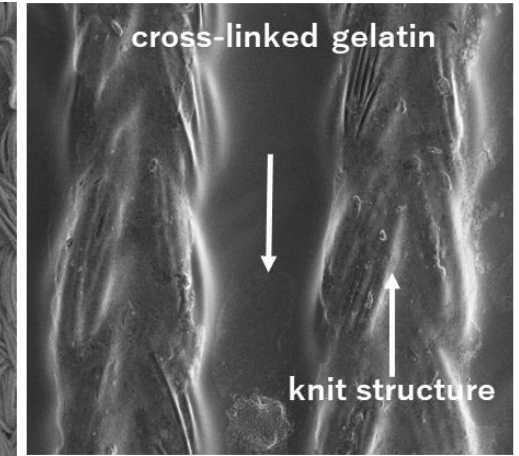
Completion of PLLA degradation
completed up to 24months (Molecular Weight, maximal strength)



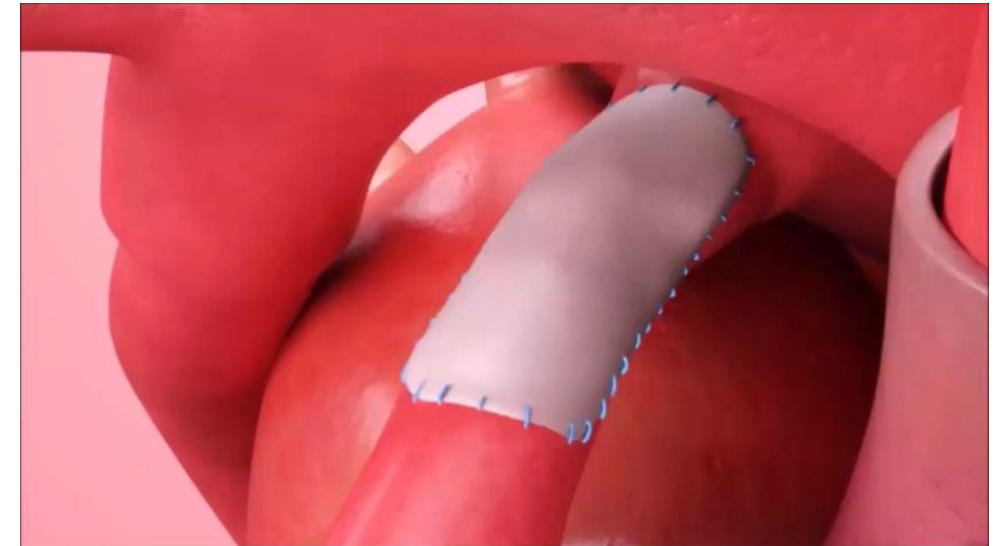
SEM



low power field



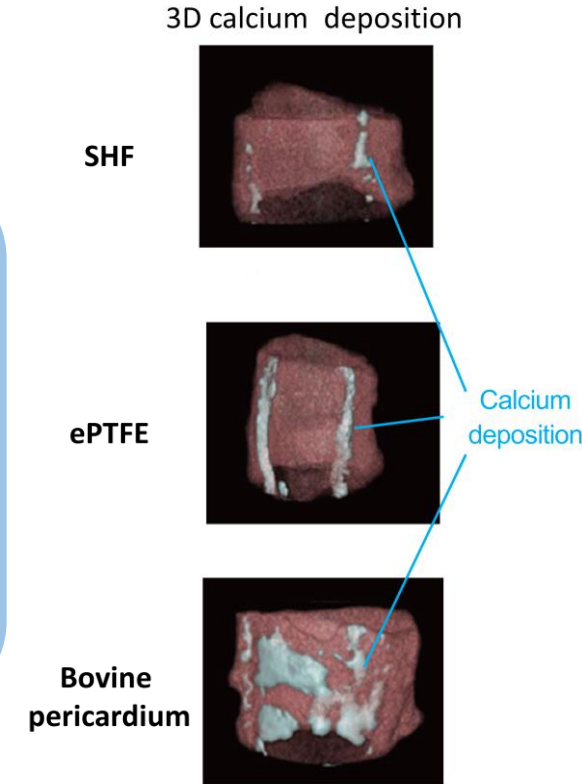
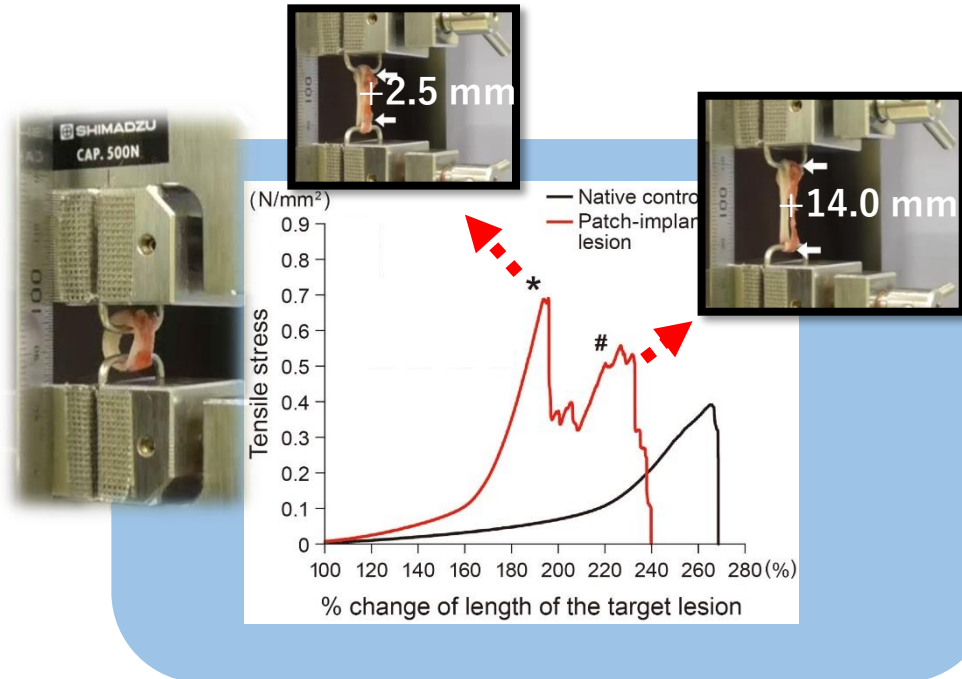
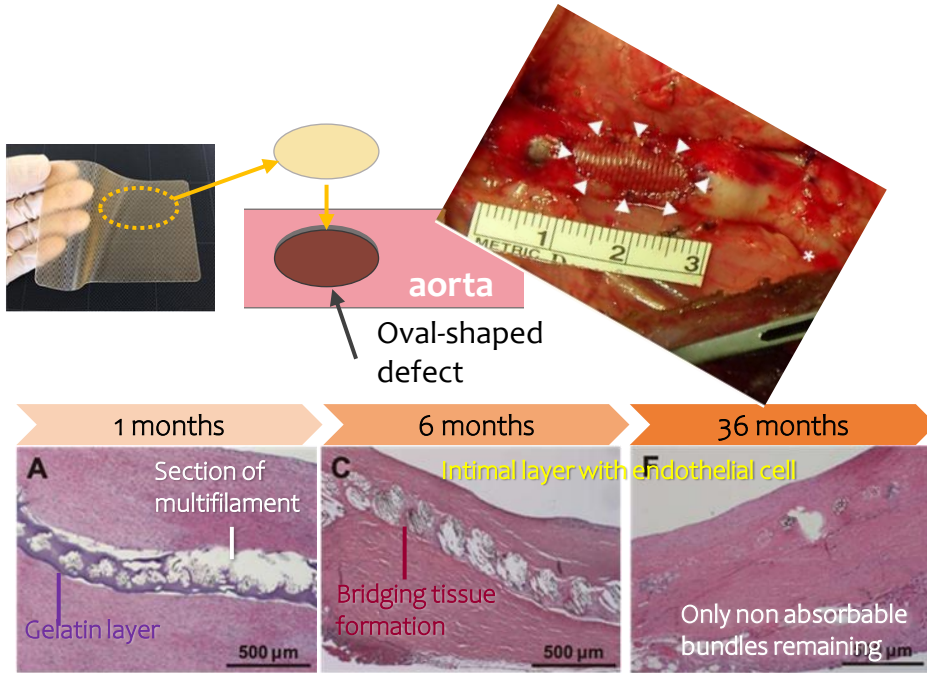
high power field





Summary of pre-clinical POC

Implantation of OFT-G1 in the canine descending aorta



S. Nemoto, et al, European Journal of Cardio-Thoracic Surgery 2018; 54:318-327
 S. Nemoto, et al, Interactive CardioVascular and Thoracic Surgery 2021; 26:165-171

- Living self-tissue regeneration
- No inflammation, no foreign body reaction
- No fibro-intimal proliferation

- Maintain mechanical strength
- Expandability

- No calcification
- Good durability

Clinical study: protocol

★ Multistage support from the regulatory authority, PMDA and MHLW

Cohort 1

First in Human, N=3

- Only Ventricular Septal Defect (VSD) patch closure (low risk)

Seamless transition

Judged by The Data Monitoring Committee (DMC)

Review 1-month postoperative course of the 3 subjects

Cohort 2

Pivotal study, N=31

- A various type of surgery except very high-risk procedure
- No limitation of the anatomical lesions of the implantation
- Enrolment from infants to adults

Primary endpoint

Surgical success* rate at one year after operation.

*No occurrence of death and re-intervention due to failure of OFT-G1

Secondary endpoints

Occurrence of residual lesions detected by echocardiography and adverse events (AE)

**After 1 year
for approval**

**After 3 years
Final evaluation**

- Utilization of multiple consultation provided by PMDA
- OFT-G1 project is designated for **“SAKIGAKE”** program to provide special support by PMDA along with the regular consultation for the earliest practical application of innovative medical products in Japan .

Study cites: May 2019~

★ Active involvement from academia for successful clinical trial

The Japanese Society of Pediatric Cardiology and Cardiac Surgery (JSPCCS) offers collaborations for clinical studies and trials.

National Cerebral and Cardiovascular Center



Hajime Ichikawa, M.D., Ph. D

*Affiliation at commencement of this clinical trial.

Current Affiliation: Japan Community Health care Organization Osaka Hospital

Okayama University Hospital



Shingo Kasahara, M.D., Ph. D



Fukuoka Children's Hospital



Toshihide Nakano, M.D., Ph. D

The University of Tokyo Hospital



Yasutaka Hirata, M.D., Ph. D

Tokyo Metropolitan Children's Medical Center

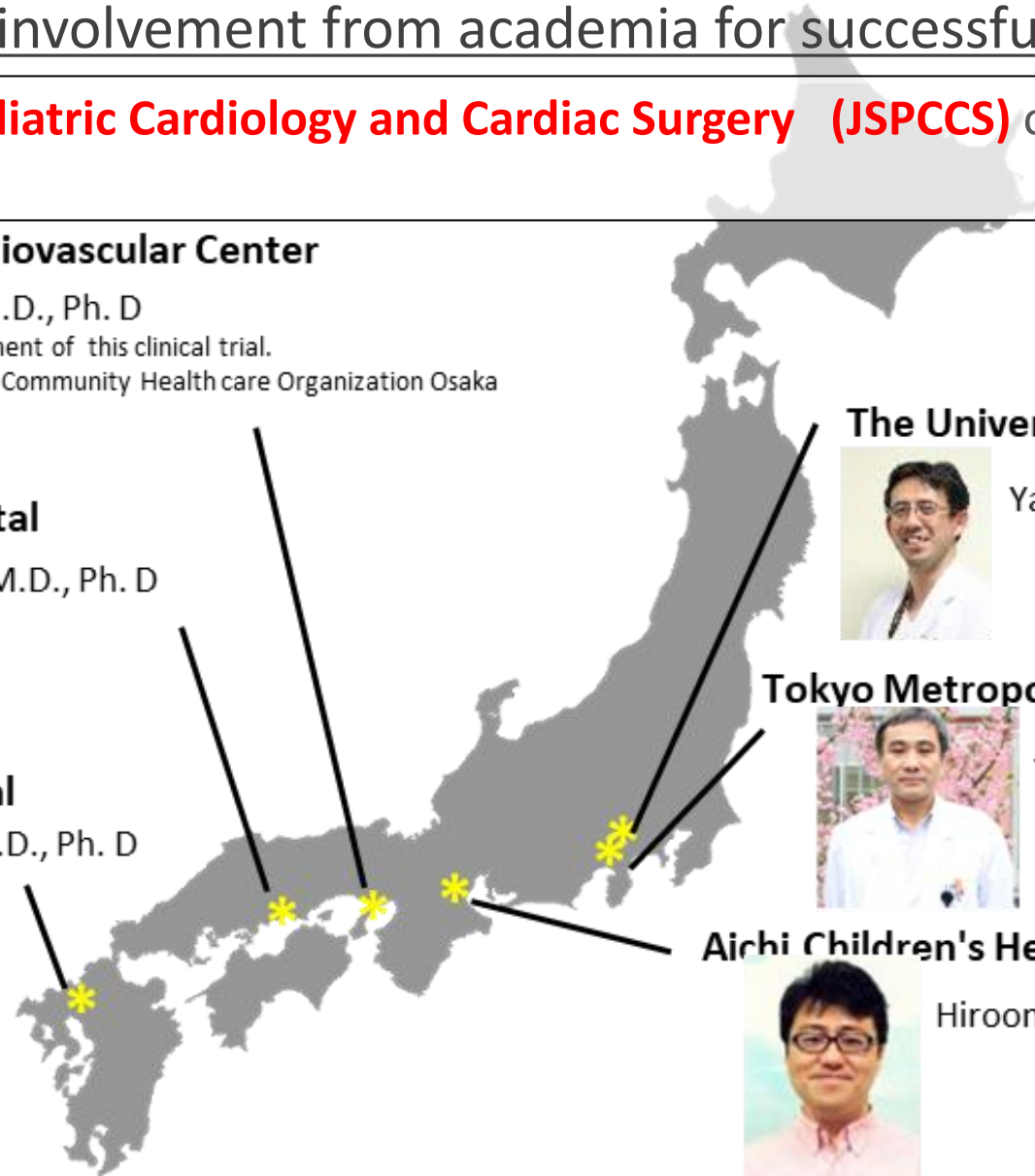


Yukihiro Yoshimura, M.D., Ph. D

Aichi Children's Health and Medical Center

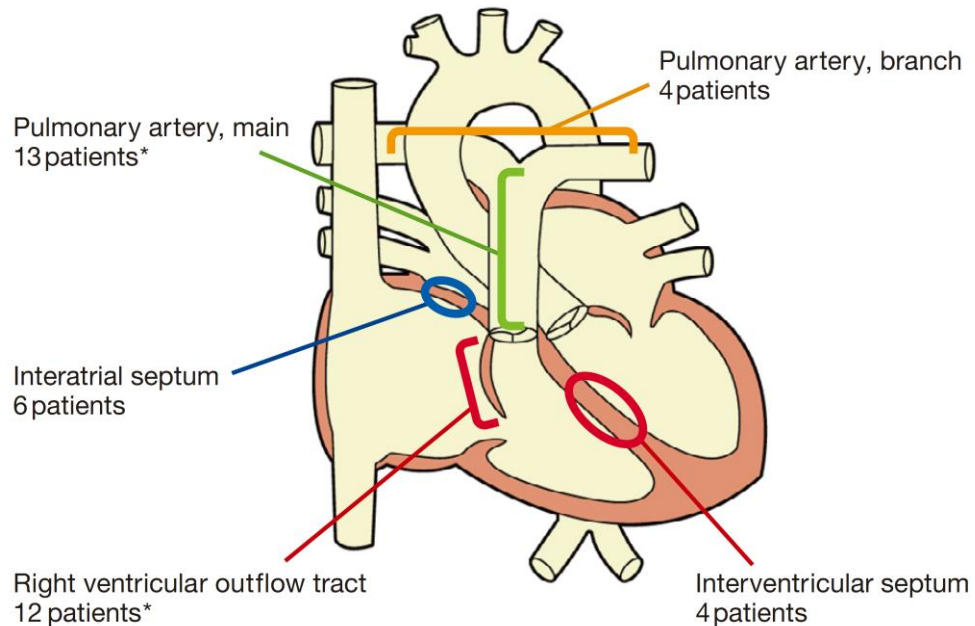


Hiroomi Murayama, M.D.

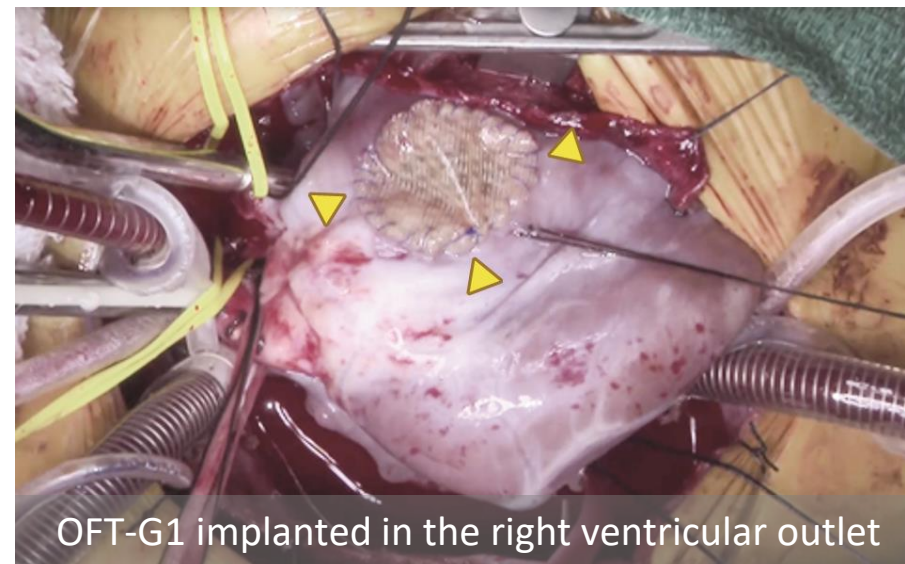


Clinical study: results

- May 23, 2019(FPI) ~ December 24, 2021(LPO)
- 34 subjects, 27 children & 7 adults
- Wide variety of cardiac anomalies



<Diagram of the OFT-G1 implantation site>



Primary endpoint

The surgical success rate at one year after operation 100.0% (90%CI: 91.6-100.0%) > the pre-defined threshold 84%

Secondary endpoints

1 Residual PA stenosis (mild, no need intervention)

Adverse event

None to be "related" or "probably related" to OFT-G1

Registered trade name & mark

Jan, 2023 – filed the application for manufacturing and sales in Japan

Only 6 months by “SAKIGAKE”

July, 2023 – approved and registered !



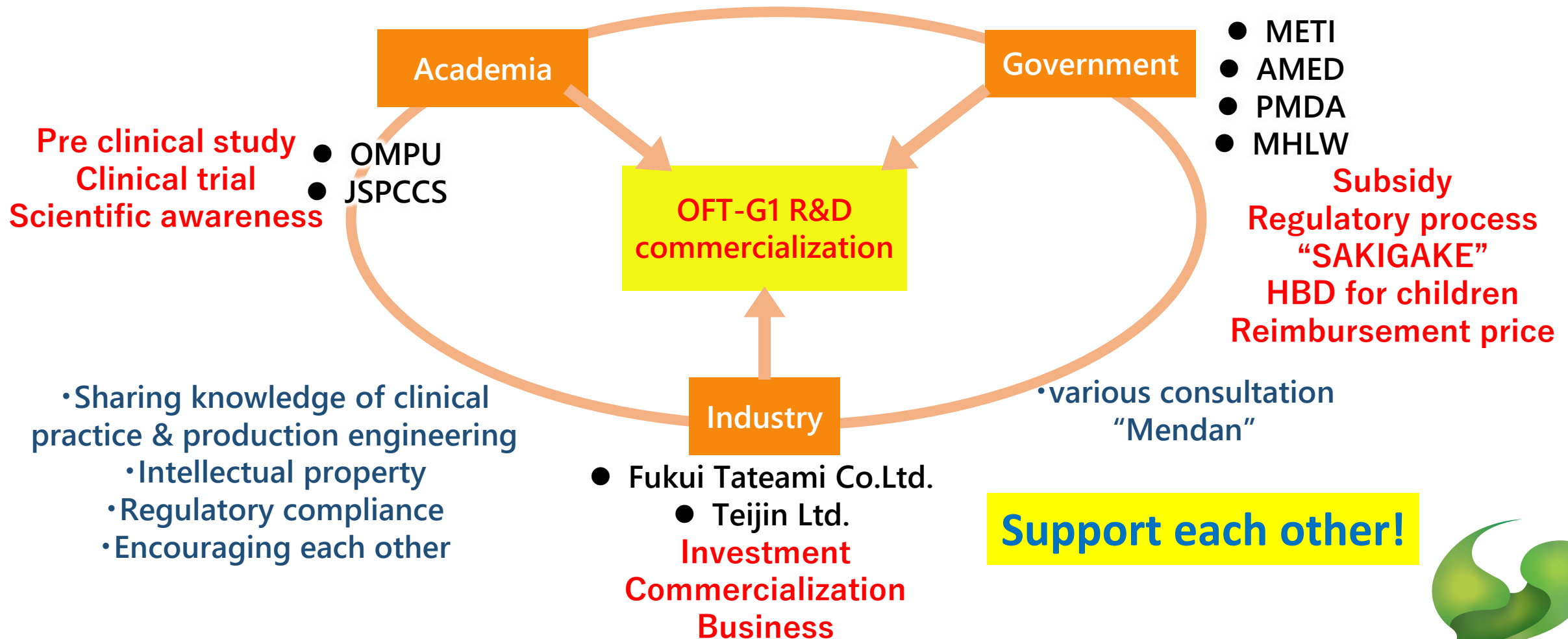
SYNFOLIUM®

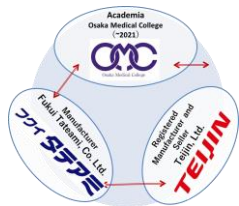
“along with”
“together”

“leaf”

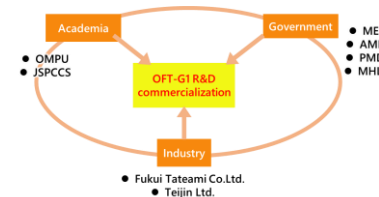
Harmonizing industry-academia-government collaboration

- Sharing understanding preclinical study result & clinical practice
- Negotiating acceptable clinical trial protocol





Contrail of OFT-G1 R&D



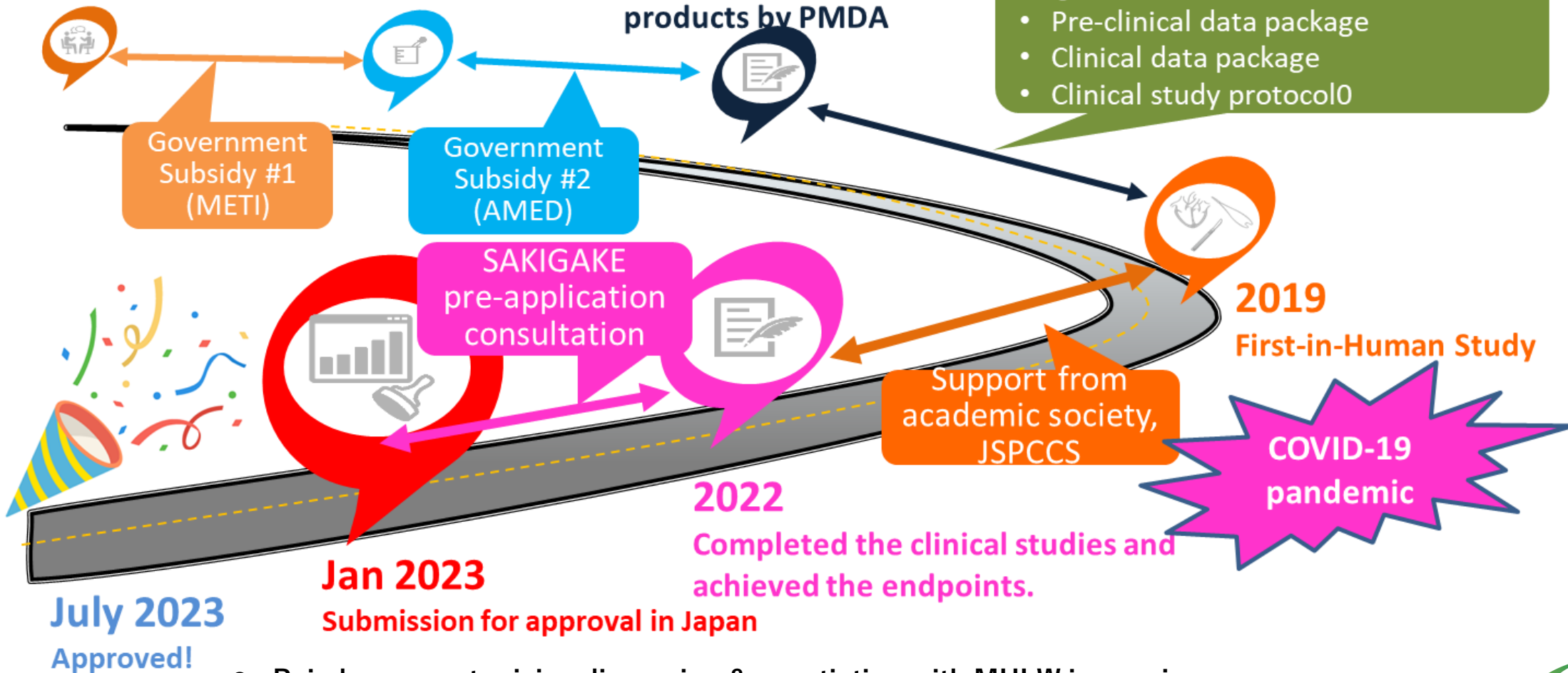
2014
Start the project

2015~2017
Design verification

2018
Designated as **SAKIGAKE** products by PMDA

Regular Consultation with PMDA

- Pre-clinical data package
- Clinical data package
- Clinical study protocol



- Reimbursement pricing discussion & negotiation with MHLW is ongoing.
- Non-GCP clinical research for additional 2 years follow-up (i.e., 5 years follow-up in total) will start accordingly.
- Previous dataplus planned post-marketing surveillance (N=150) can be additional clinical evidences of SYNFOLIUM.



To obtain FDA approval!

FDA – PMDA initiative for medical device development
US-Japan I-A-G collaboration = HBD (& HBD for children)



Harmonizing By Doing



Real HBD - Dinner @ CRT23 in D.C., February 26, 2023

Communication with FDA



1st unofficial Meeting (Feb, 27 2023, face to face)

- Initial engagement to introduce SYNFOLIUM (OFT-G1) to FDA
- Agreed to have continuous discussion for US registration

2nd unofficial Meeting (Jun 8 2023, Web)

- Discussions and feedbacks on;
- Device classification of SYNFOLIUM
- Adequacy of Clinical study data conducted in Japan for US registration

3rd unofficial Meeting (Aug 29 2023, face to face)

- Discussions and feedbacks on;
- Gap analysis of preclinical data package
- Requirement of Human Factor study
- Alignment of the key topics of Pre-submission Meeting

FDA Pre-submission MTG (planned early 2024)

- Teijin will apply FDA Pre-submission MTG to ensure official feedbacks from FDA;
- Preclinical data package
- Clinical data package
- Regulatory submission pathway

**All comments and feedbacks from FDA at unofficial meetings are non-binding*

Worldwide recognition and market development



**WCPCCS 2023 Washington
Aug 28 – Sept 1, 2023**

**EACTS 2023 Vienna
Oct 4 – 7, 2023**



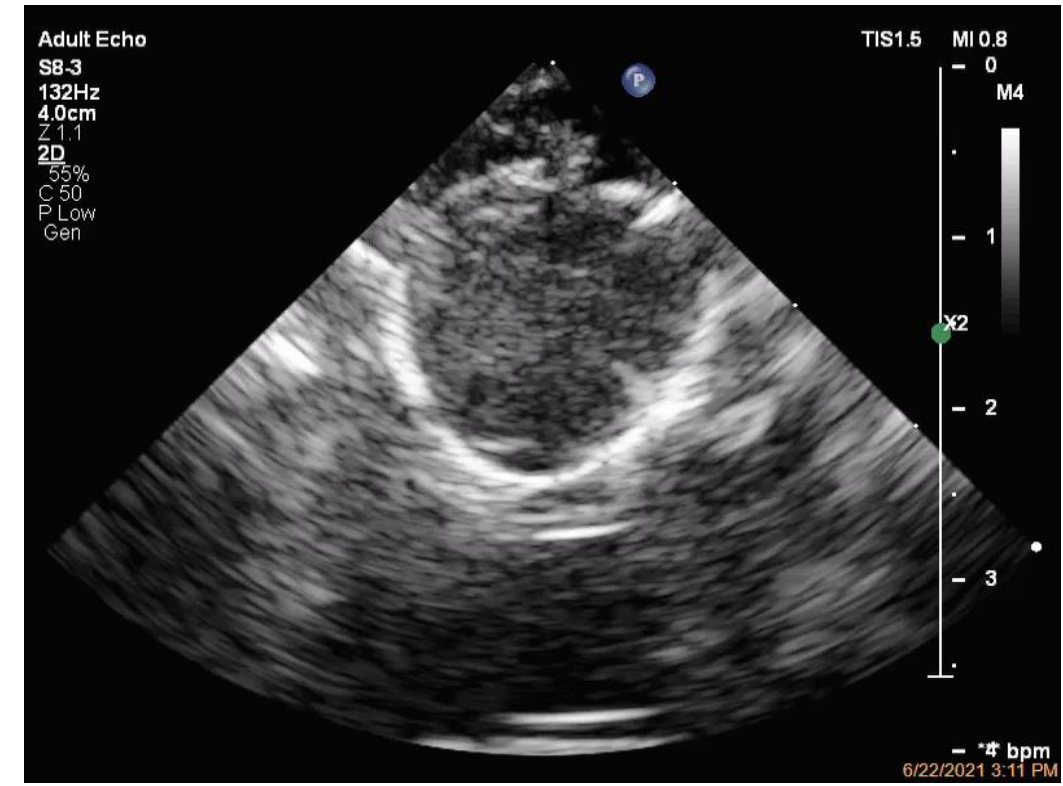
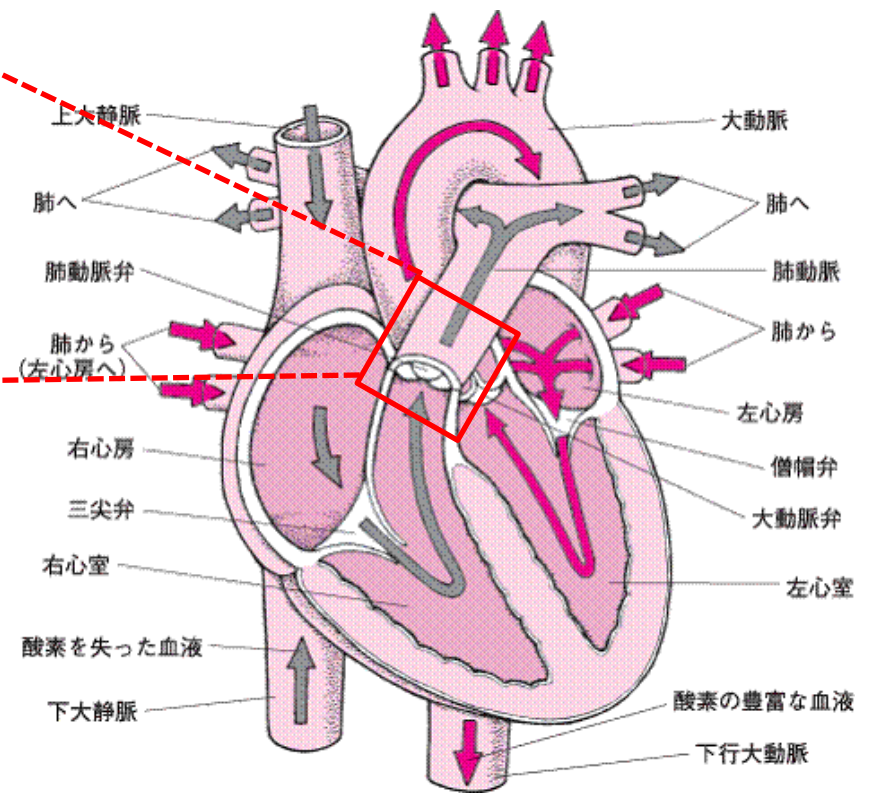
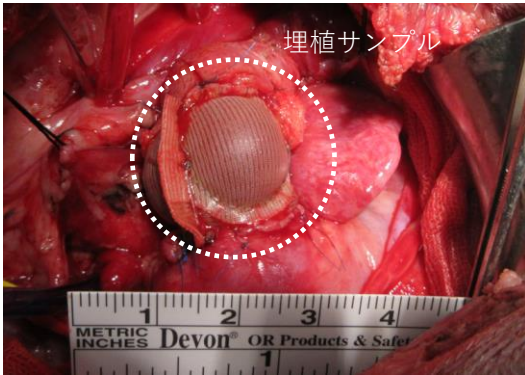
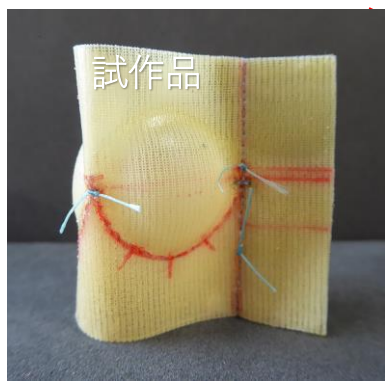
Challenges in expanding overseas:

- Establish alliance with partner companies (Size? Need R&D function? Only distribution?)
- Complex reimbursement pricing in the US
- Apply for EU CE marking & obtain certification



Further development using OFT-G1 technology

Ongoing another challenge



I would like to express my gratitude to all the members involved in the industry-academia-government collaboration in this OFT-G1 development.

