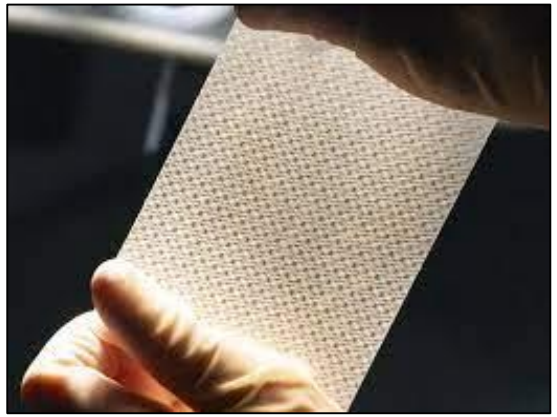
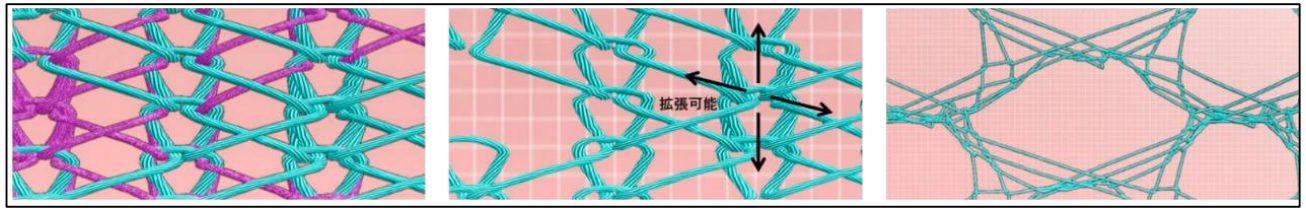
The road from development to approval of pediatric medical devices and future approach “SYNFOLIUM®” for congenital cardiac surgery





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.

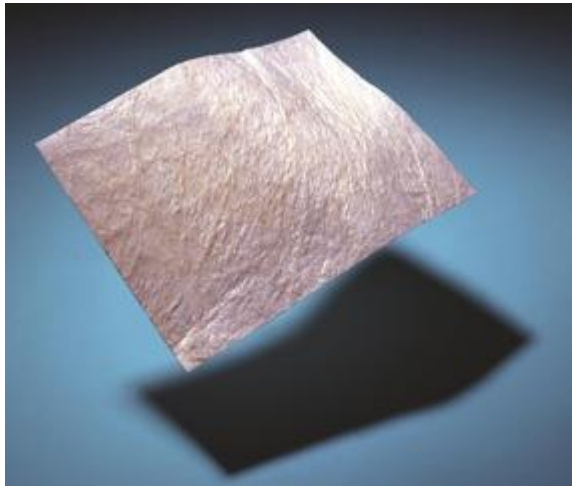
- Those materials **can not be expandable** to be matched to the body size.

⇒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/cardiocel-bioscaffold-patch

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

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

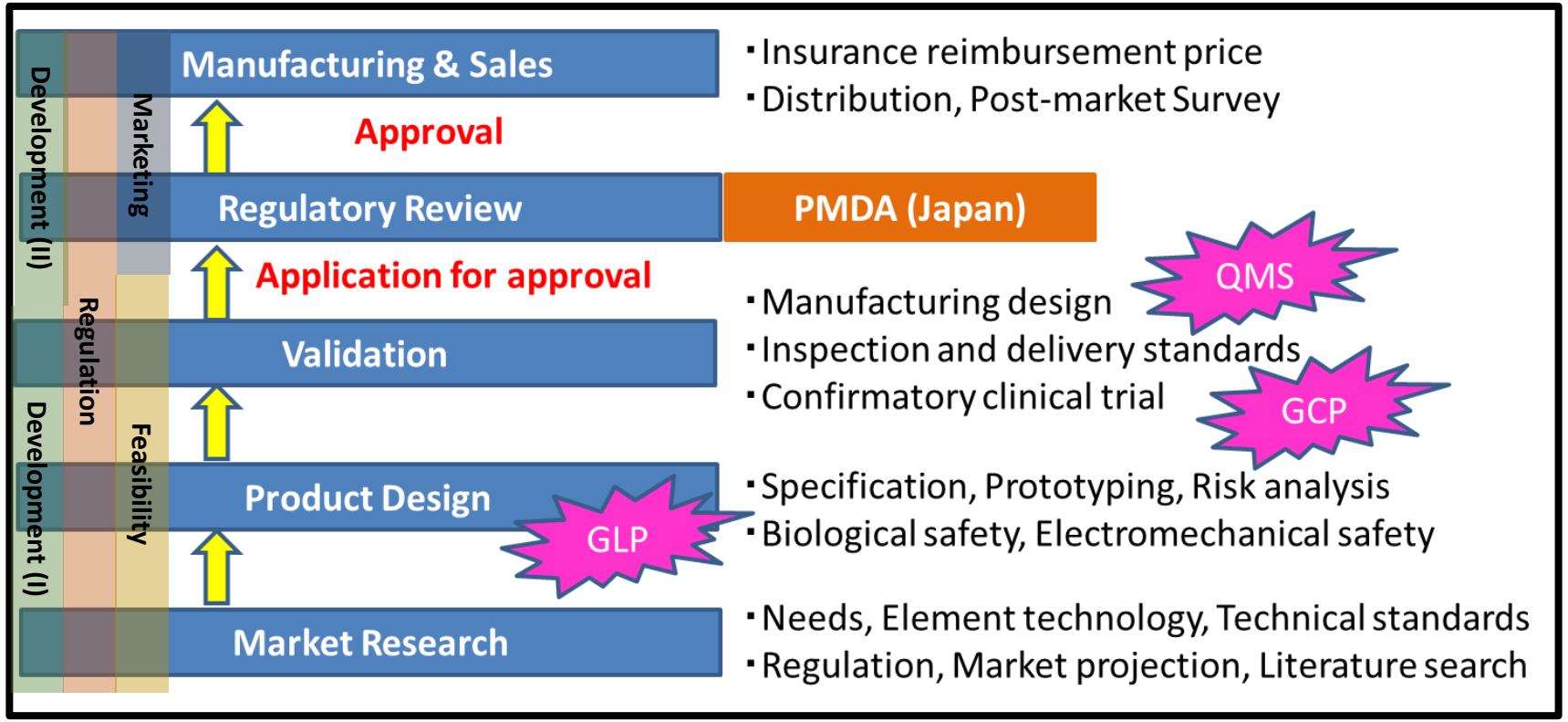
https://xeltis.com/xeltis-initiates-first-ever-pivotal-trial-of-a-synthetic-restorative-pulmonary-heart-valve/

✓ **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



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!

Technology?
Intellectual Property?

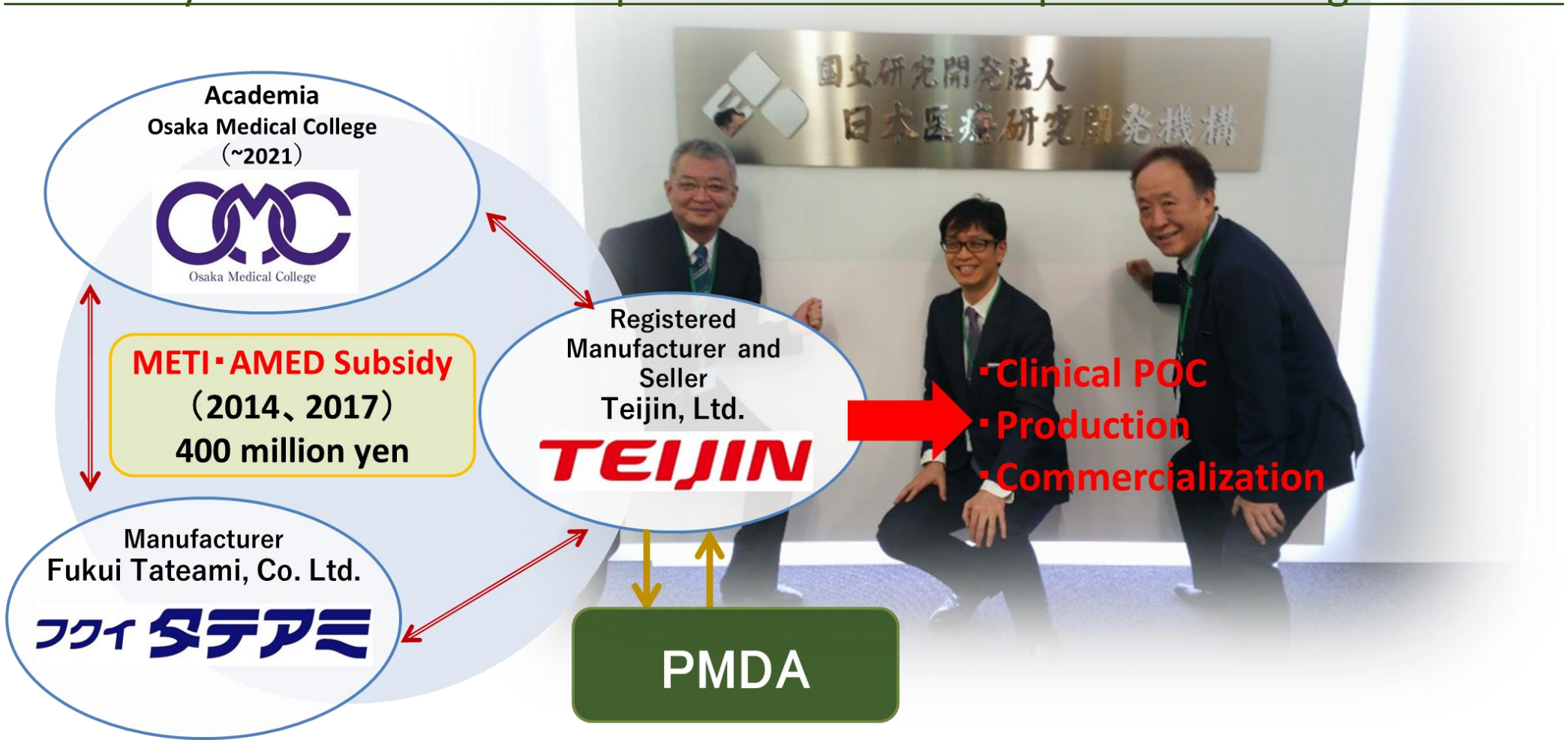
Sterilization?
Production?
Logistics?

POC?
Regulation?
Reimbursement?

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

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

Osaka Medical College

フクイ タテアミ

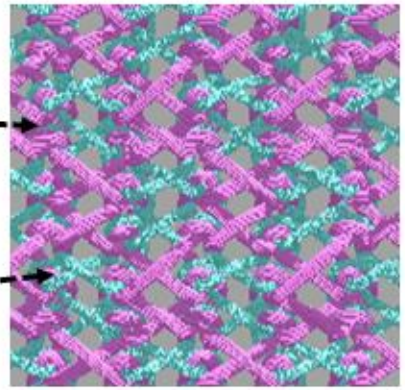
TEIJIN

- **Industrial technology PT** — product standard, sterilization
- **Intellectual property PT** — patents, scientific output
- **Preclinical, Regulatory compliance, Safety PT** — GLP, PMDA → **Clinical PT** — GCP, PMDA, academia society (JSPCCS)
- **Manufacturing quality control PT** — GMP, QMS, Packaging, logistics
- **Sales PT** — reimburse price, trademark registration, domestic, international

Concept & Component of OFT-G1 (code name)

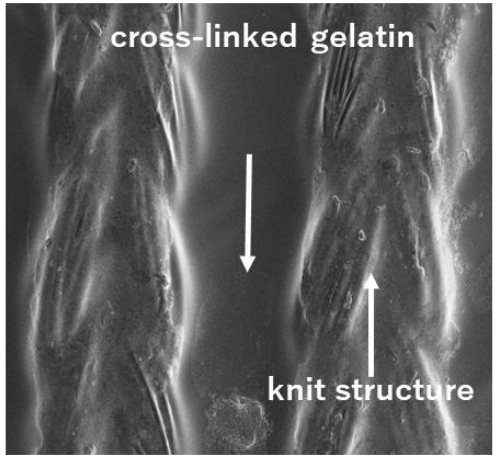
Biodegradable (PLA) yarn acts as **hooks**

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



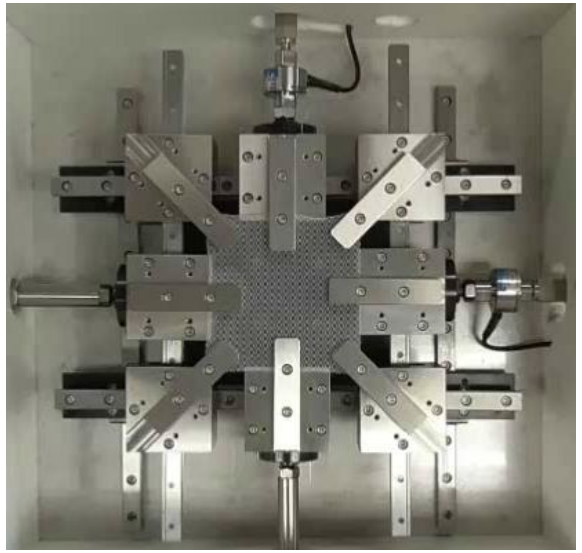
SEM

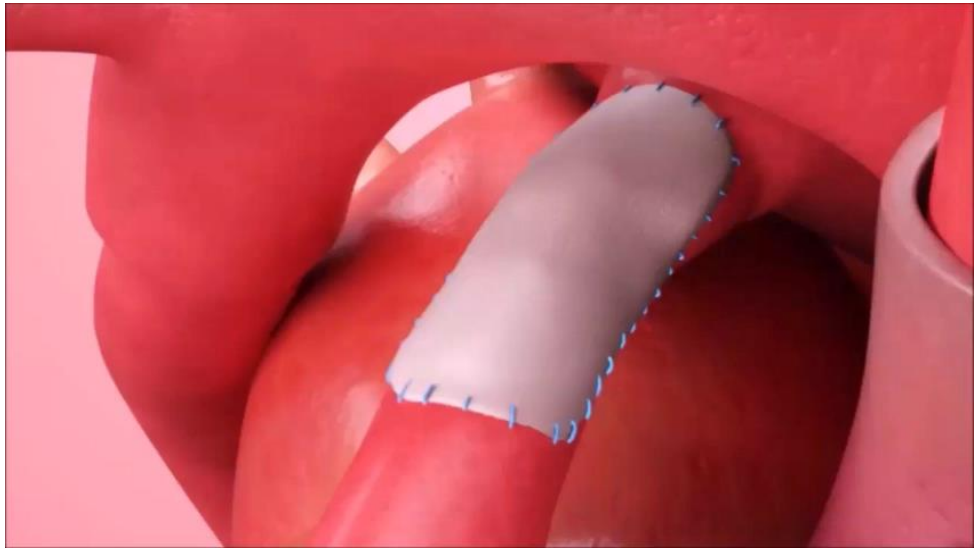
low power field



high power field

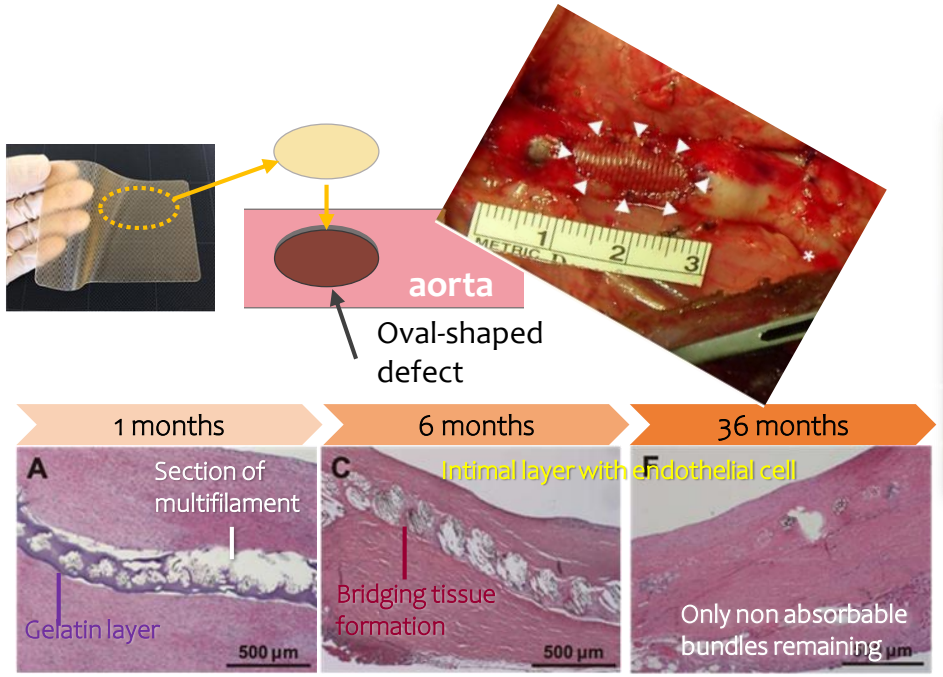
Completion of PLLA degradation
completed up to 24months (Molecular Weight, maximal strength)

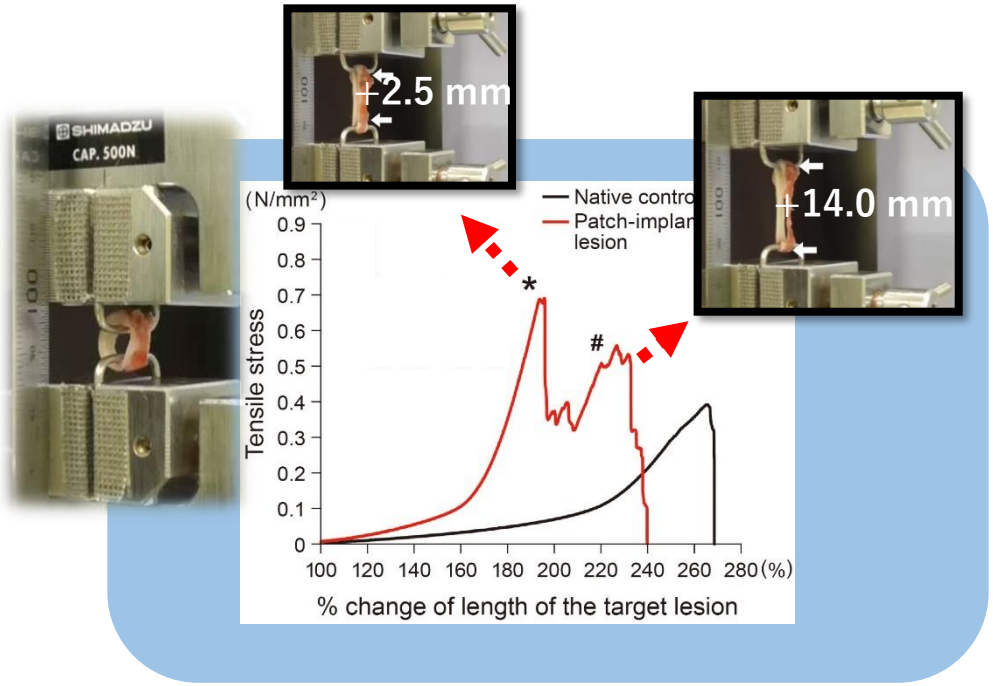


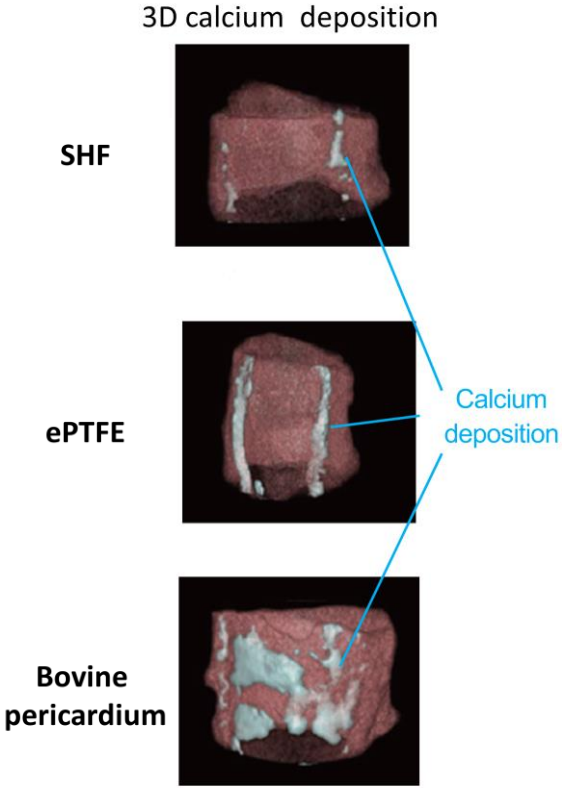


Summary of pre-clinical POC

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

After 1 year for approval

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 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

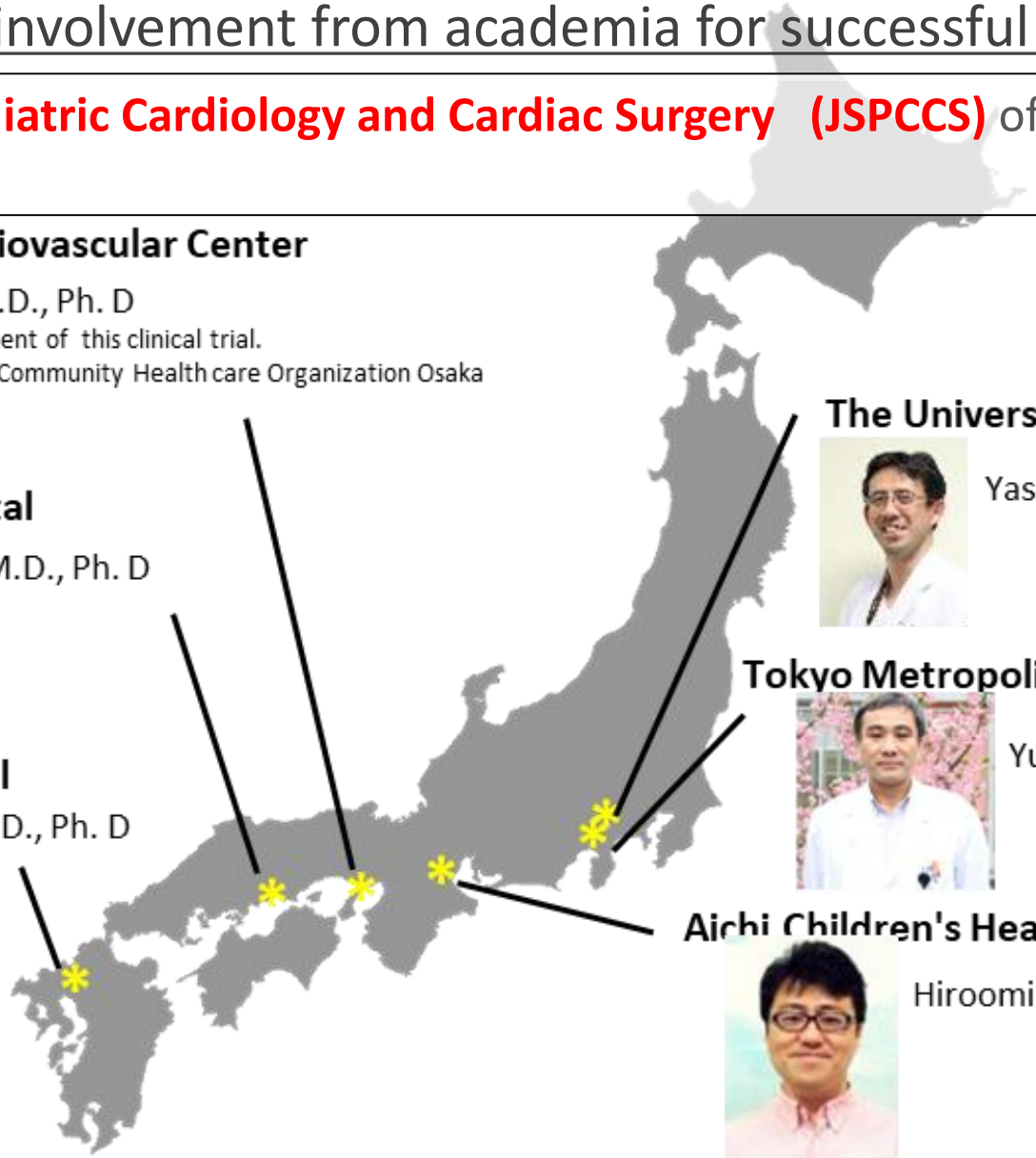
*Affiliation at commencement of this clinical trial.
Current Affiliation: Japan Community Health care Organization Osaka Hospital

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

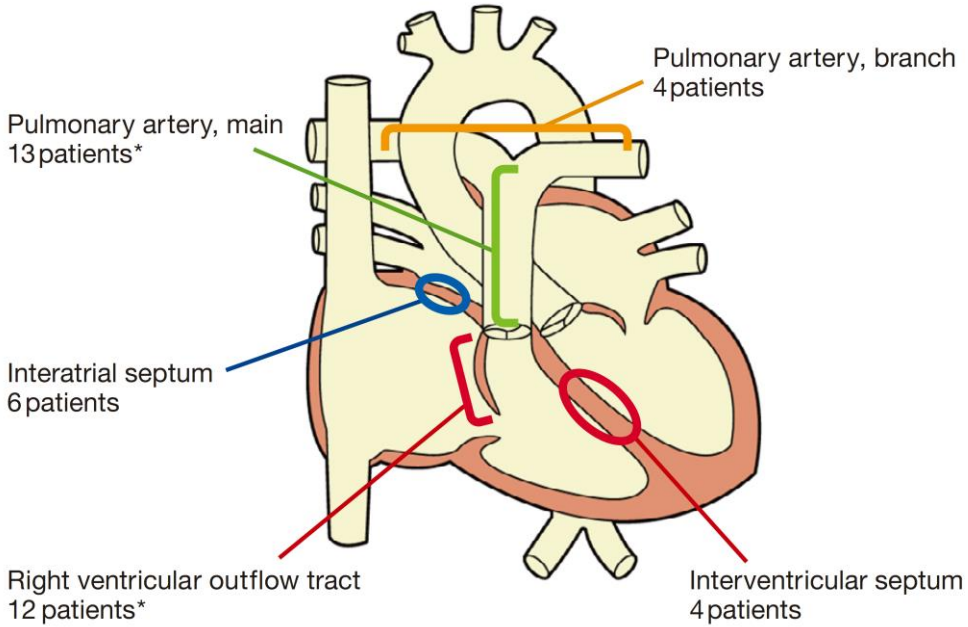
Yukihiro Yoshimura, M.D., Ph. D

Aichi Children's Health and Medical Center

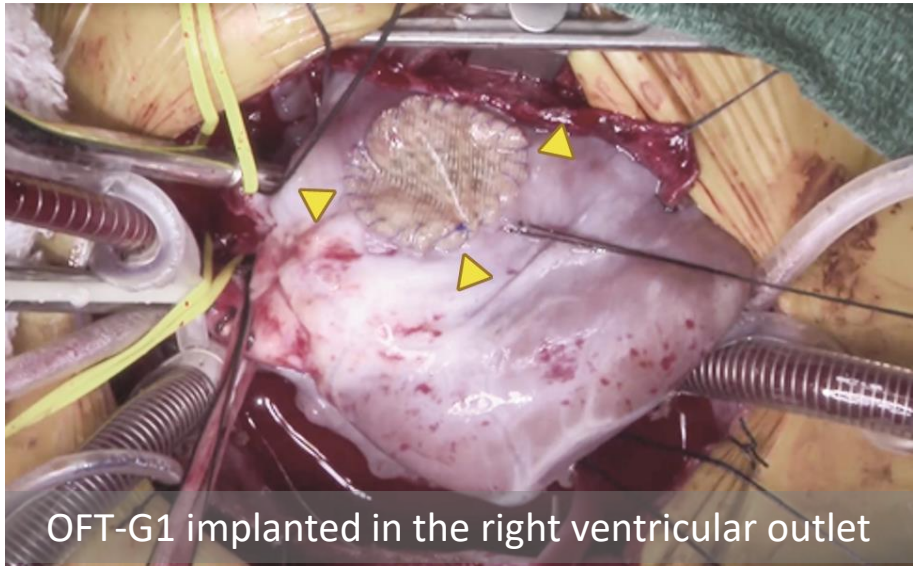
Hiroomi Murayama, M.D.

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-G1implantation site>


OFT-G1 implanted in the right ventricular outlet

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

Academia

Pre clinical study
Clinical trial
Scientific awareness

- OMPU
- JSPCCS

Government

- METI
- AMED
- PMDA
- MHLW

Subsidy
Regulatory process
"SAKIGAKE"
HBD for children
Reimbursement price

OFT-G1 R&D commercialization

Industry

・Sharing knowledge of clinical practice & production engineering
・Intellectual property
・Regulatory compliance
・Encouraging each other

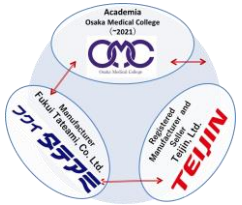
- Fukui Tateami Co.Ltd.
- Teijin Ltd.

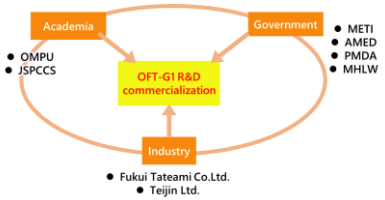
Investment
Commercialization
Business

・various consultation
"Mendan"

Support each other!

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 protocol0

Government Subsidy #1 (METI)

Government Subsidy #2 (AMED)

SAKIGAKE pre-application consultation

2019
First-in-Human Study

Support from academic society, JSPCCS

COVID-19 pandemic

2022
Completed the clinical studies and achieved the endpoints.

Jan 2023
Submission for approval in Japan

July 2023
Approved!

- 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 data plus 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 **B**y **D**oing

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)

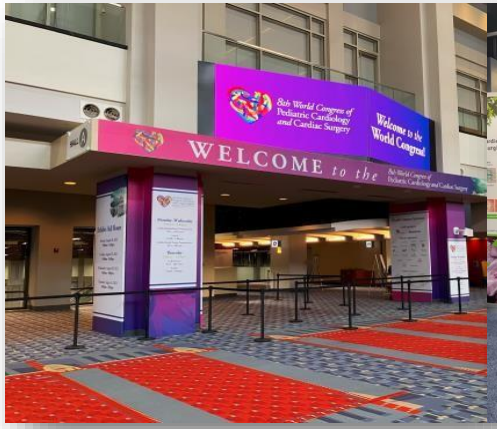
Discussions and feedbacks on;
- Gap analysis of preclinical data package
- Requirement of Human Factor study
- Alignment of the key topics of Pre-submission Meeting

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

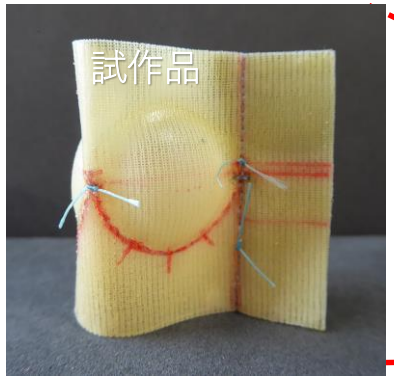
EACTS 2023 Vienna
Oct 4 – 7, 2023

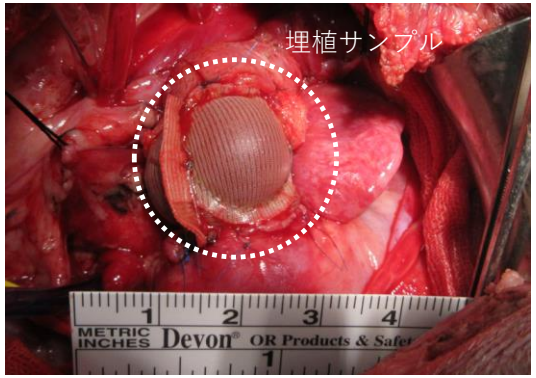
<u>Challenges in expanding overseas:</u>

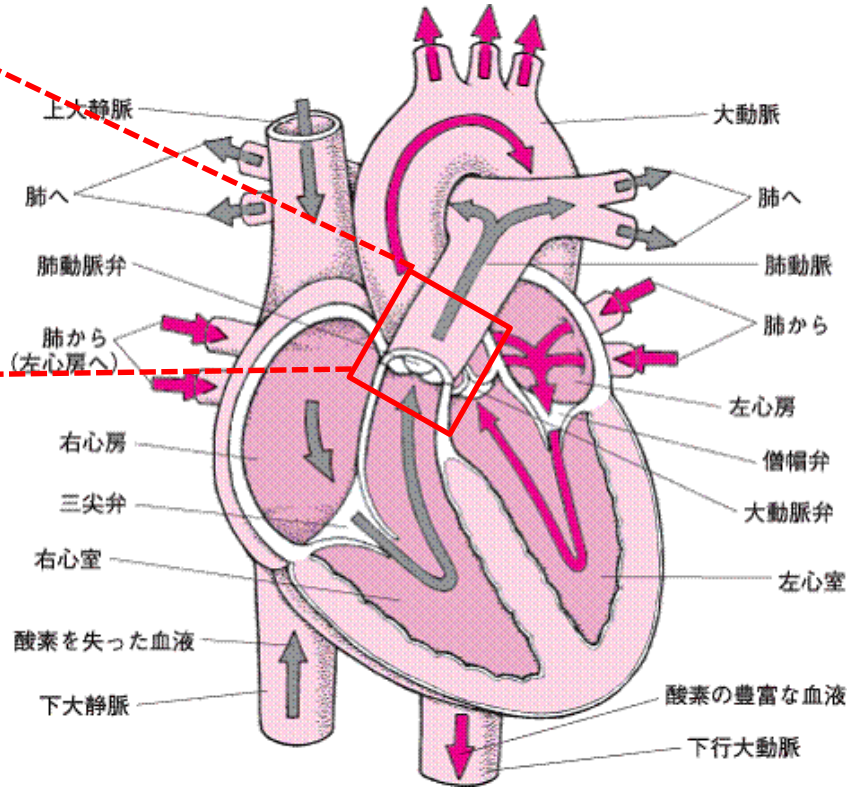
- **Establish alliance with partner companies (Size? Need R&D function? Only distribution?)**
- **Complex reimbursement pricing in the US**
- **Apply for EU CE marking & obtain certification**

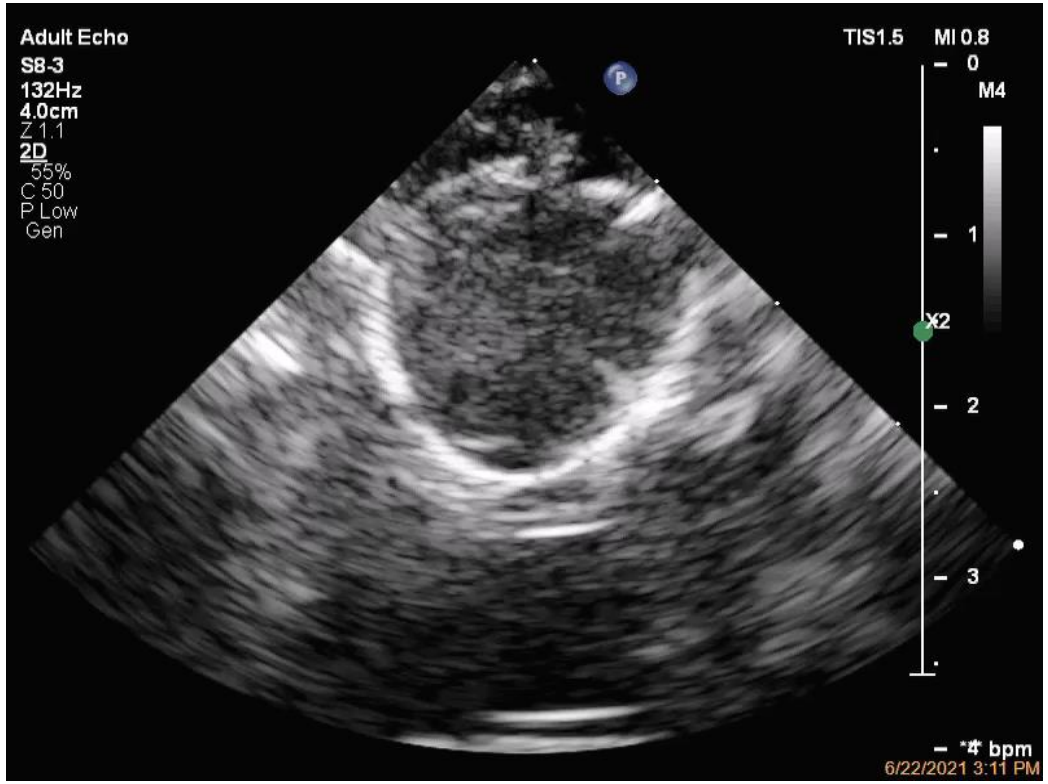
Further development using OFT-G1 technology

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.