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DIPS 1000+ Project, 2023 Tech Conference

The Japanese Government's Research and Development Support System for Induced Pluripotent Stem Cell (iPSC)-Based Therapies

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Vice-Chair, Database Committee, Japanese Society for Regenerative Medicine

DISCLAIMER

The views and opinions expressed in this presentation are those of the presenter and do not necessarily represent the official policy or position of the Japan National Institute of Health Sciences, the Japan Ministry of Health, Labour & Welfare.

Also, the presenter has no COI to disclose with this presentation.

AGENDA

1. Current Status of Clinical Applications of iPSC-derived Products in Japan

2. R&D Support for iPSC-derived Products by Japan Agency for Medical Research & Development (AMED)

3. Regulatory Science on Emerging Safety Issues for iPSC-derived Products

4. NRMD: National Patient Registry System for Clinical Research and Post-Marketing Surveillance on Cell Therapy Products

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Clinical Applications of iPSC/ESC-Derived Products in Japan

in Non-Commercial Clinical Researches under the RM Safety Act and Commercial Clinical Trials under the PMD ACT

As of October 21, 2023; ** According to a newspaper report

Final Product	Starting Cells	Target Disease	Institution(s)	Type of Clinical Trial	IMP Approval	FIH Trial
Retinal pigment epithelial cells	*Autologous iPSCs*	Exudative age-related macular degeneration	FBRI, RIKEN	Non-commercial clinical research under the RM Safety Act	2013	2014
Retinal pigment epithelial cells	Allogeneic iPSCs	Exudative age-related macular degeneration	Kobe City Medical Center, Osaka Univ., Kyoto Univ., RIKEN	Non-commercial clinical research under the RM Safety Act	2017	2017
Dopaminergic neural progenitor cells	Allogeneic iPSCs	Parkinson's disease	Kyoto Univ.	Clinical trial under the PMD Act	2018	2018
Platelets	*Autologous iPSCs*	Aplastic anemia	Kyoto Univ.	Non-commercial clinical research under the RM Safety Act	2018	2019
Corneal epithelial cells	Allogeneic iPSCs	Corneal epithelial stem cell exhaustion	Osaka Univ.	Non-commercial clinical research under the RM Safety Act	2019	2019
Hepatocytes	*ESCs (Allogeneic)*	Congenital urea cycle disorder	NCCHD	Clinical trial under the PMD Act	2019	2019
Cardiomyocytes	Allogeneic iPSCs	Ischemic cardiomyopathy	Osaka Univ.	Clinical trial under the PMD Act	2019	2020
Neural progenitor cells	Allogeneic iPSCs	Subacute spinal cord injury	Keio Univ. etc.	Non-commercial clinical research under the RM Safety Act	2019	2021
Retinal photoreceptor cells	Allogeneic iPSCs	Retinitis pigmentosa	Kobe City Eye Hospital	Non-commercial clinical research under the RM Safety Act	2020	2020
NKT cells	Allogeneic iPSCs	Recurrent or advanced head and neck cancer	Chiba Univ., RIKEN	Clinical trial under the PMD Act	2020	2020
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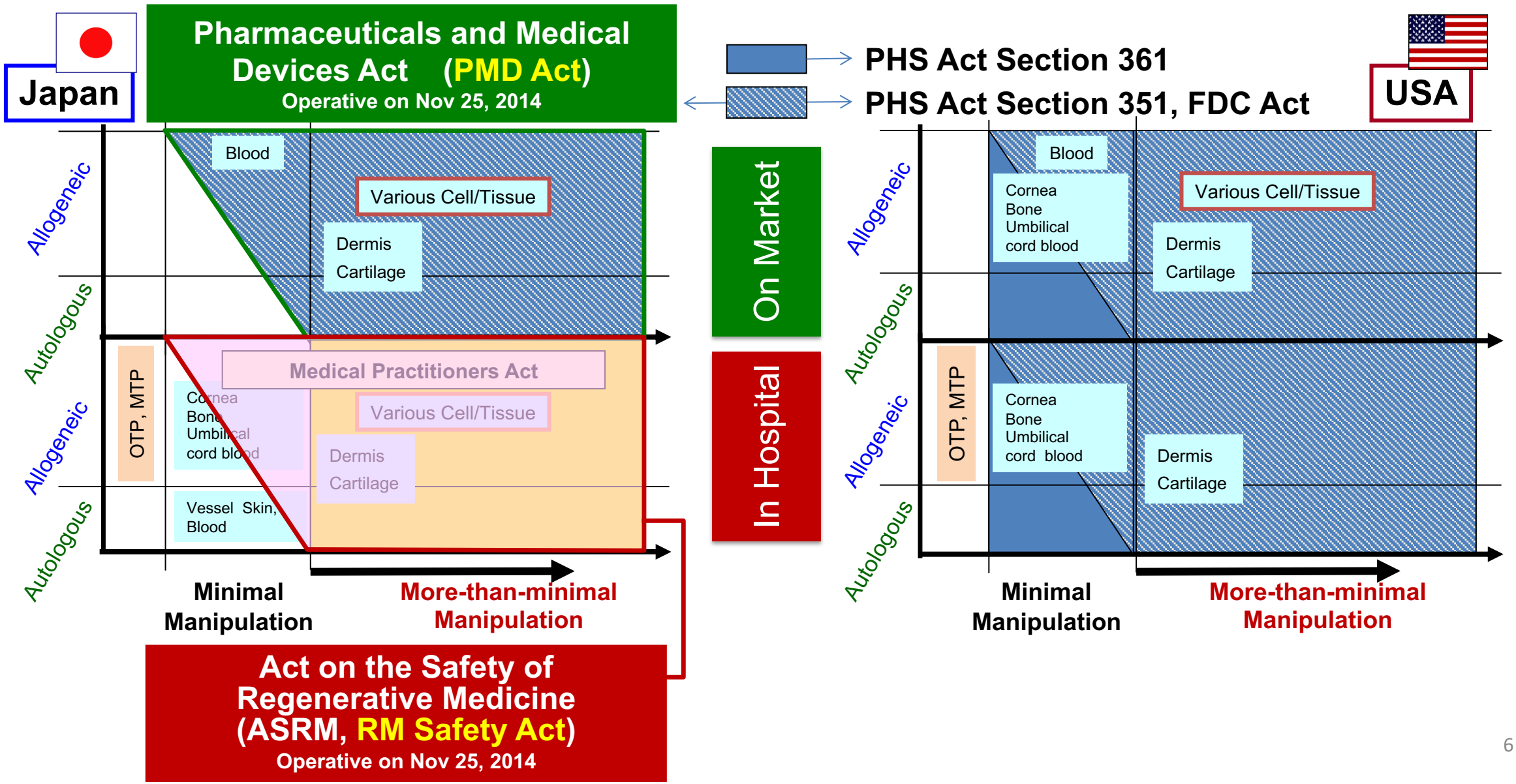
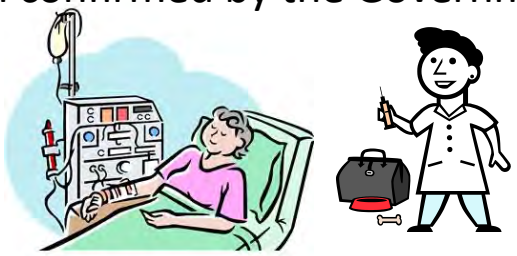
Regulations for Regenerative Medicine and Cell Therapy



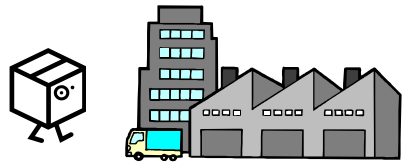
Two Acts Regulating RM/CT

Regenerative Medicine (RM)
Cell Therapy (CT)

Medical practices using processed cells, whose safety and efficacy have not yet been confirmed by the Government



Manufacturing and marketing of **products for RM/CT** by firms



Act on the Safety of Regenerative Medicine (RM Safety Act)

- Medical treatments using processed cells
- Clinical researches using processed cells (non-commercial)

Pharmaceuticals & Medical Devices Act (PMD Act)

- Regenerative medical products (RMPs=CTP/GTPs)
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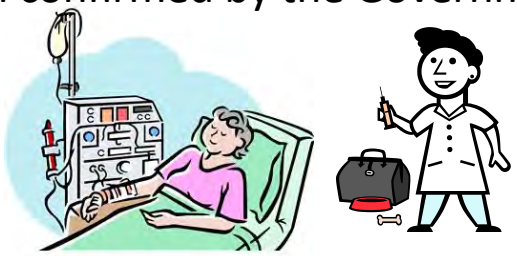

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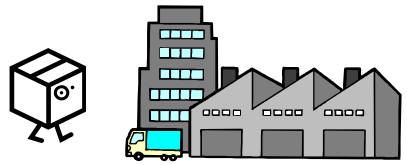

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Protection of the Public Health through the RM Safety Act (since 2014)

6 arrested over unauthorized stem cell therapy using cord blood

KYODO NEWS August 27, 2017

MATSUYAMA, Japan – Police on Sunday arrested a doctor and five others suspected of involvement in unauthorized stem cell therapies using blood from umbilical cords and placenta after childbirth.

The doctor who heads a clinic in Tokyo and people involved in cord blood sales are suspected to have administered cord blood to seven patients to treat cancer and as a beauty treatment. Each treatment is said to have cost 3 million to 4 million yen ($27,400-$36,600).

While hopes are high over the use of cord blood in the field of regenerative medicine to treat a number of diseases as it contains stem cells, the health ministry is concerned over the spread of costly medical services provided without clear scientific evidence and without ensuring sufficient safety.

The arrests were the first of anyone suspected of violating a law on regenerative medicine that came into force in 2014. The transplantation of cells could involve the risk of graft rejection and infection.

edical institutions using stem cells are required to submit treatment plans beforehand review by the health ministry, except for treating designated diseases such as kemia.

The six suspects allegedly conducted the treatments without notifying the authorities.

Based on the RM Safety Act, the Government can arrest medical practitioners who perform **cell therapy without notifying the authorities in order to prevent future adverse events.**

https://english.kyodonews.net/news/2017/08/5d0a5ee3cba3-update1-6-arrested-over-unauthorized-stem-cell-therapy-using-cord-blood.html

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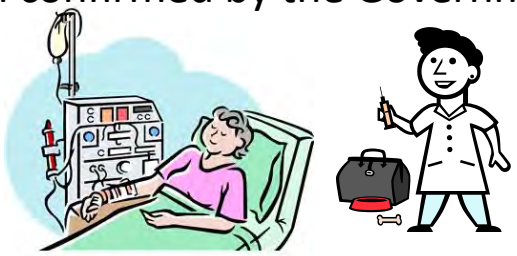

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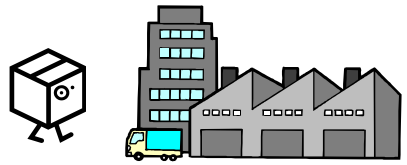

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“RM/CT as Medical Care” vs. “Products for RM/CT (& GT)”

	RM/CT as Medical Practices	Products for RM/CT (&GT)
Purpose	Ensuring the safety and validity of **medical treatments AND non-commercial clinical researches** using processed cells	Development, manufacturing & marketing of **regenerative medical products (RMPs = CTPs & GTPs)**
Regulatory Framework	**Medical Practitioners Act & Medical Care Act** **Regenerative Medicine Safety Act (RM Safety Act)** **Ordinance for Enforcement of the Act on the Safety of Regenerative Medicine (MHLW Ordinance No. 110 (2014))**	**Pharmaceuticals & Medical Devices Act (PMD Act)** Guidelines and Standards for Ensuring the Quality/Safety of Cell-Based Therapeutic Products and Gene Therapy Products
GCTP (GMP) Compliance	**Mandatory (MHLW Ordinance No. 110 (2014))**	**Mandatory (MHLW Ordinance No. 93 (2014))**
GCP Compliance in Clinical Researches/Trials	**Not mandatory for the data system** **Mandatory for the ethical procedures (MHLW Ordinance No. 110 (2014))**	**Mandatory for clinical trials of RMPs intended for marketing (MHLW Ordinance No. 89 (2014))**
Review	**Accredited Committee for RM [Institutional] [for Class 3 RM/CT]** **Accredited Special Committee for RM [Institutional] [for Class 1 & 2 RM/CT]**	**Pharmaceuticals & Medical Devices Agency (PMDA) and Ministry of Health Labour & Welfare (MHLW)**
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Health Insurance	**NOT covered by public insurance** (Non-commercial clinical researches are covered by public research funds.)	**Fully covered by public insurance** (Commercial clinical trials are covered by private/public research funds.)

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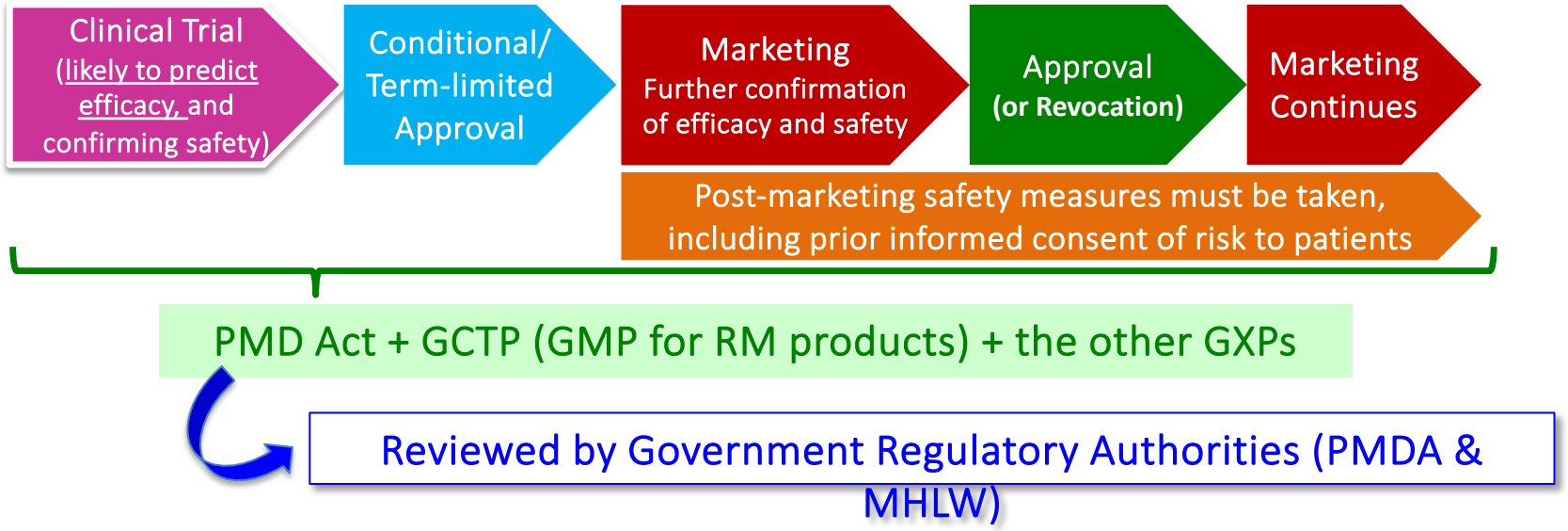
Conventional and Special Approval Systems for RM Products (CGTPs) in Japan

Conventional development pathway

Special development pathway that accommodates early practical application of RM products (CGTPs)



Conventional and Special Approval Systems for RM Products (CGTPs) in Japan

☐ Conventional development pathway

Non-commercial Clinical Research → Clinical Trial (confirmation of efficacy and safety) → Approval → Marketing

→ Similar to IND/IMP and MAA in US and EU/UK

☐ Special development pathway that accommodates early practical application of RM products (CGTPs)

Non-commercial Clinical Research → Clinical Trial (likely to predict efficacy, and confirming safety) → Conditional/ Term-limited Approval → Marketing Further confirmation of efficacy and safety → Approval (or Revocation) → Marketing Continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients

RM Safety Act (including GCTP)

PMD Act + GCTP (GMP for RM products) + the other GXPs

→ Reviewed by Government Regulatory Authorities (PMDA & MHLW)

→ Reviewed by Institutional Committees (Accredited Special Committees for Regenerative Medicine)

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1. Current Status of Clinical Applications of iPSC-derived Products in Japan

In general, it is difficult to fix product specifications and manufacturing process of CTPs, prior to the first-in-human (FIH) clinical trial. It is also difficult to change the specifications and manufacturing process after the initiation of clinical trials, because of the difficulty in demonstrating the comparability of the product quality before and after the change.

Non-commercial clinical researches on CTPs under the RM Safety Act are reviewed by government-accredited institutional committees rather than by regulatory authorities and have low-quality assurance requirements for clinical data. Therefore, this system enables low-cost and rapid initiation of FIH studies and **provides a flexible approach to optimize the quality specifications and manufacturing process based on the very early clinical findings, before initiating commercial clinical trials under the PMD Act.**

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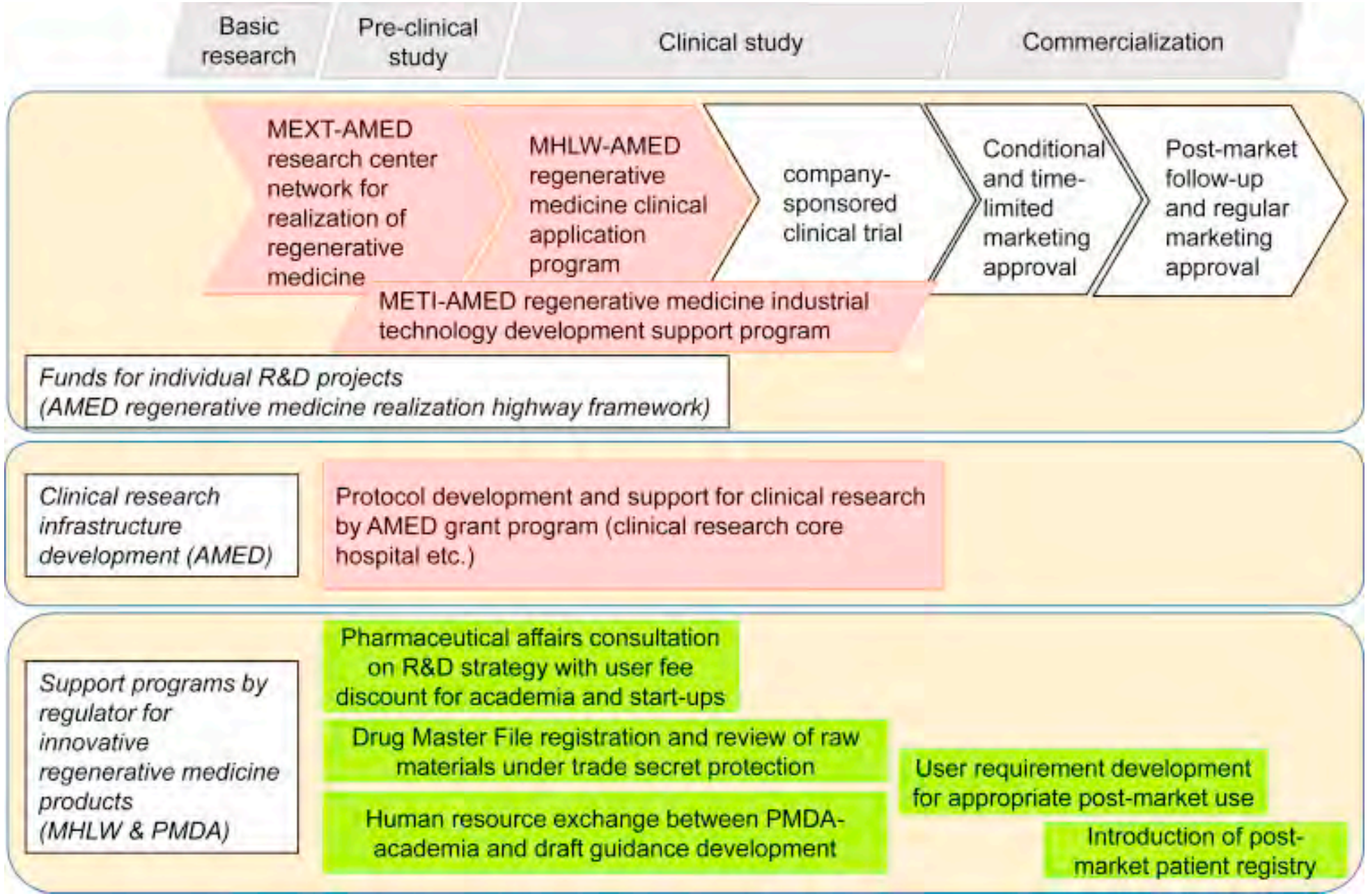
Support Programs for the R&D of RM Products/CTPs in Japan



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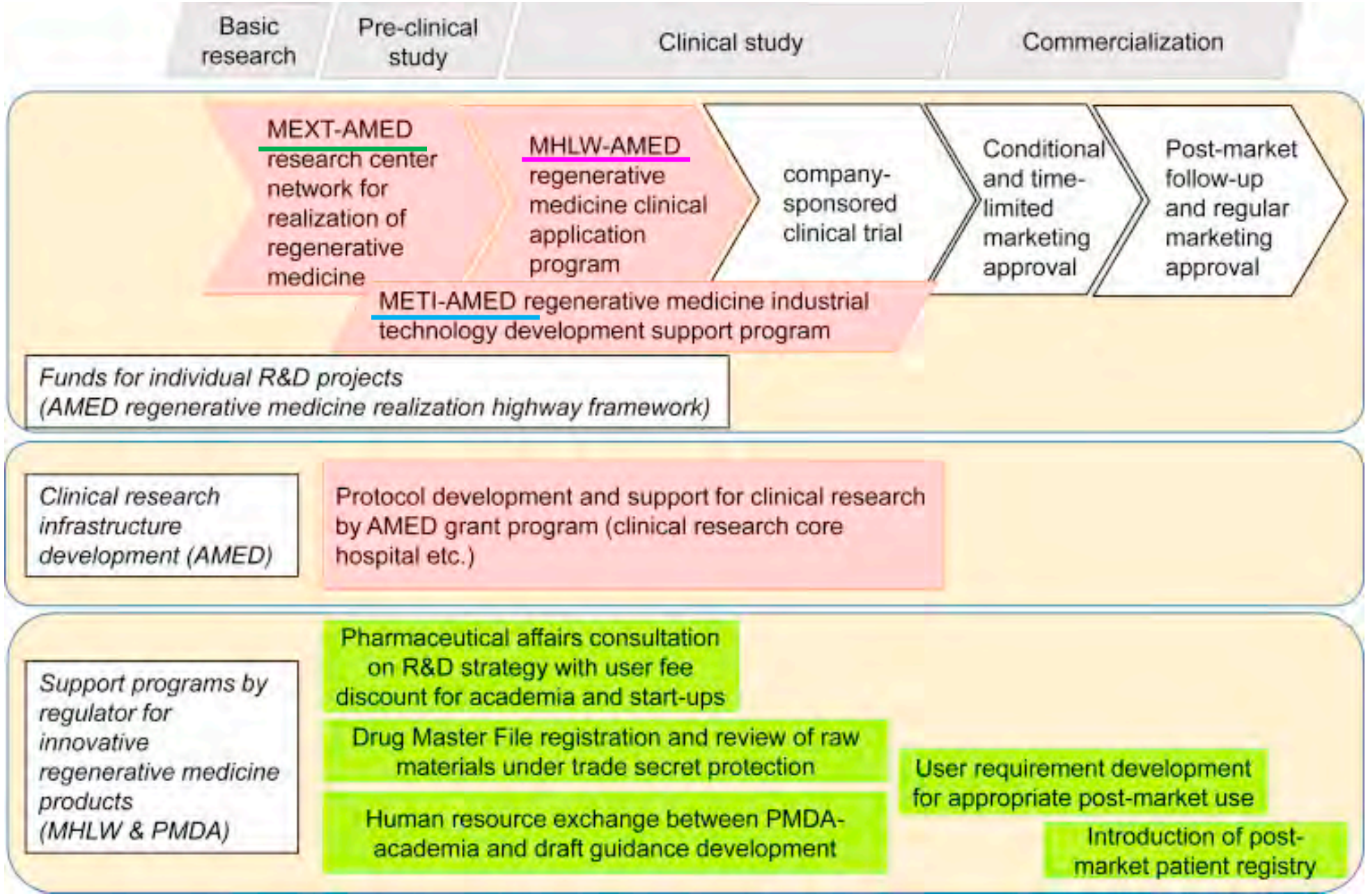

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Source: Modified from WSCS2021 presentation by Mr. Yasuji Watanabe, AMED

About AMED (Japan Agency for Medical Research and Development)

1. Objective

Promotion of medical R&D from basic research to practical applications and effective establishment/ maintenance of an environment for medical R&D

2. Established: 1st April 2015

3. Organization

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②Number of staff (as of 1st January 2022)

Number of full-time staff : 403

4. Budget (FY 2022)

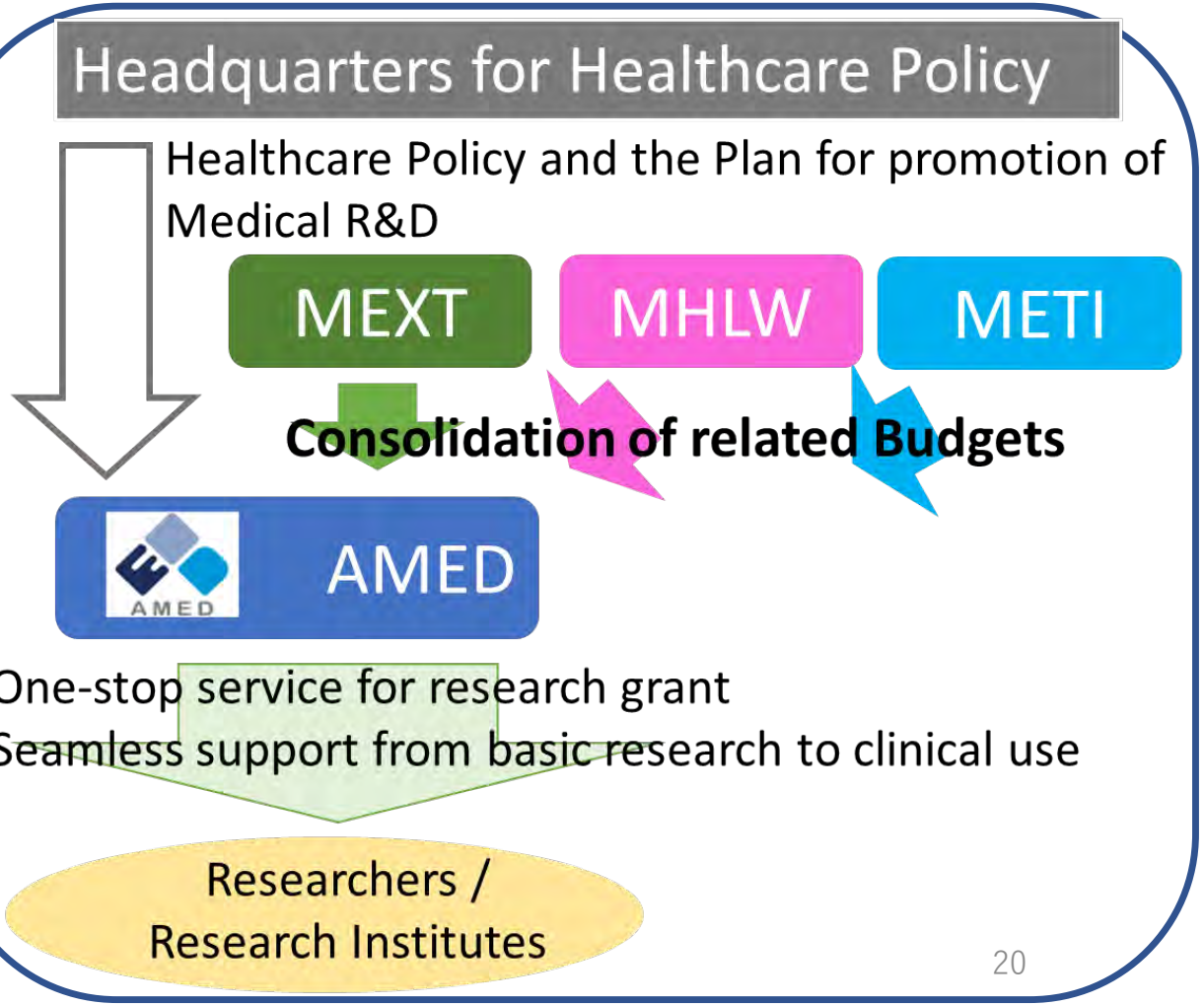
Approx. US$1B

Subsidies for AMED: 124.9 billion yen

Adjustment fund: 17.5 billion yen*

*Part of STI promotion funds are allocated

National Framework for Medical R&D since 2015



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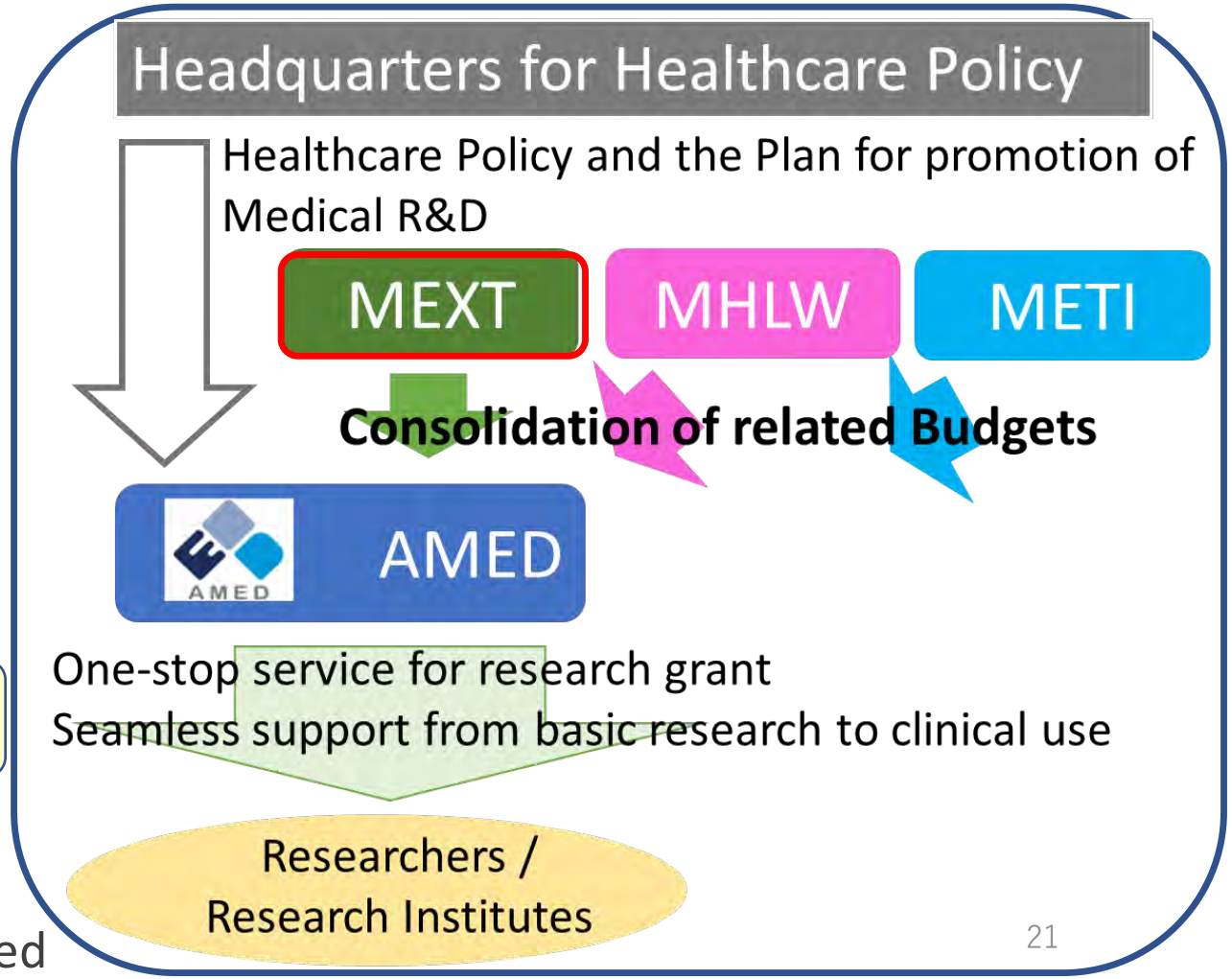

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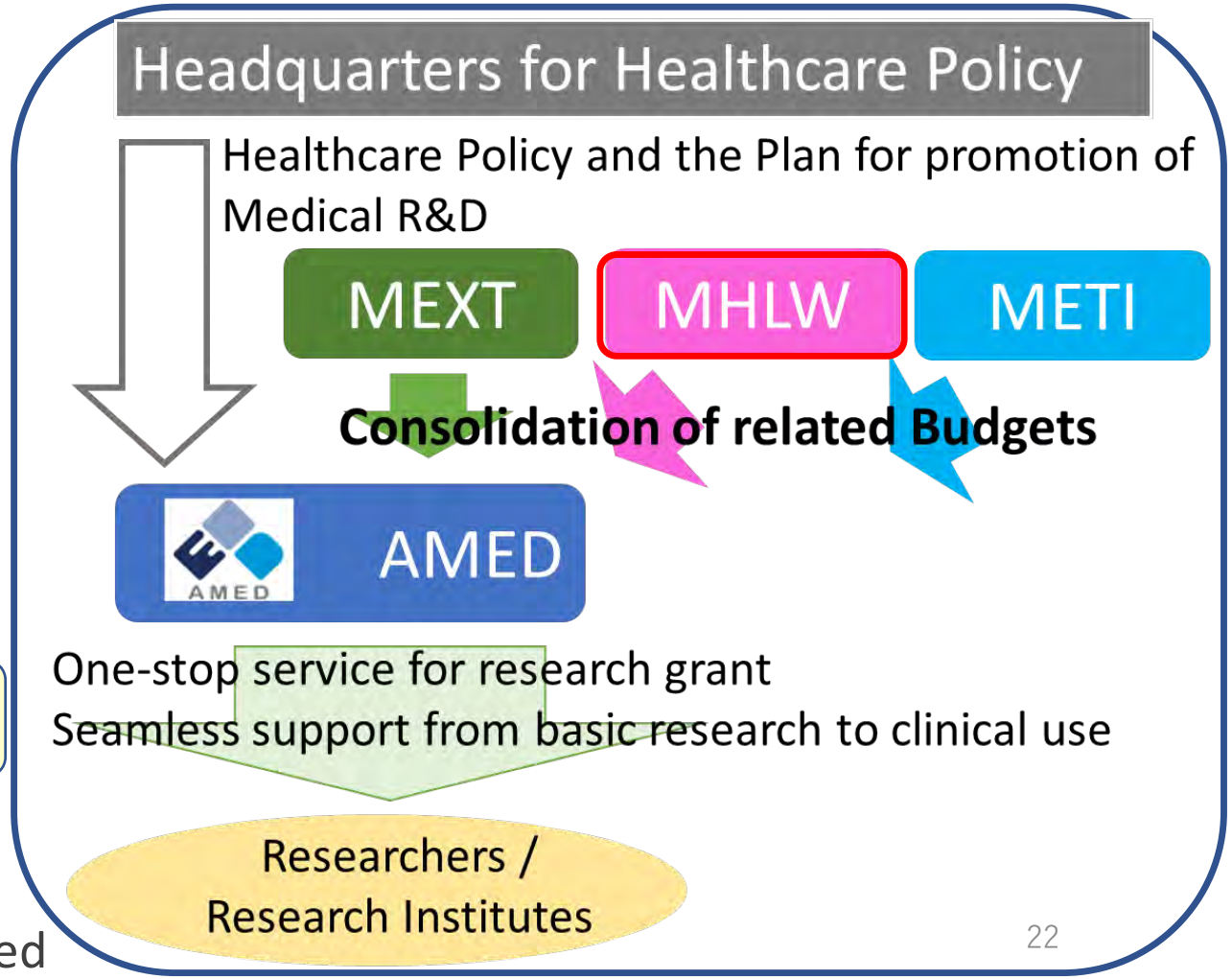

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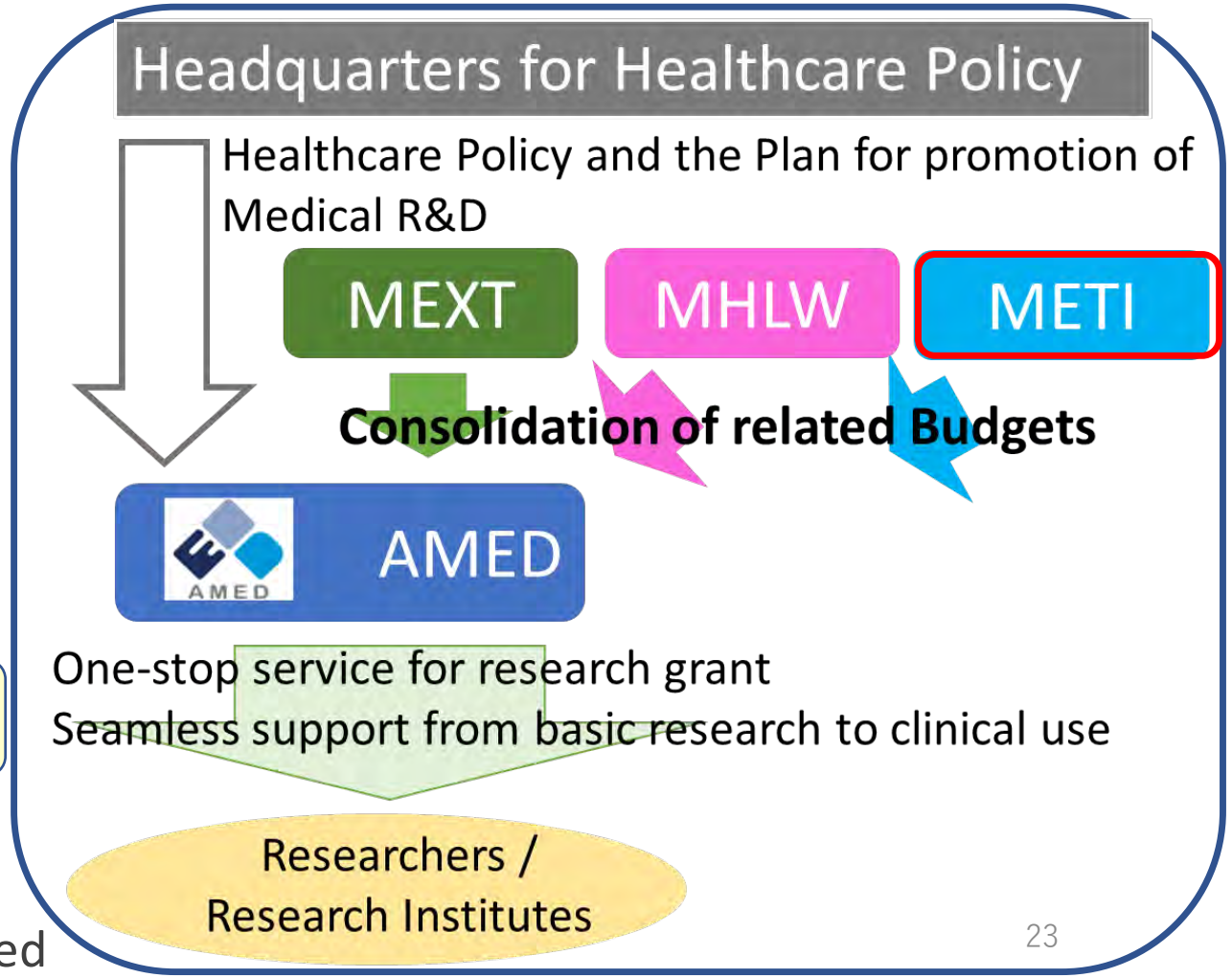

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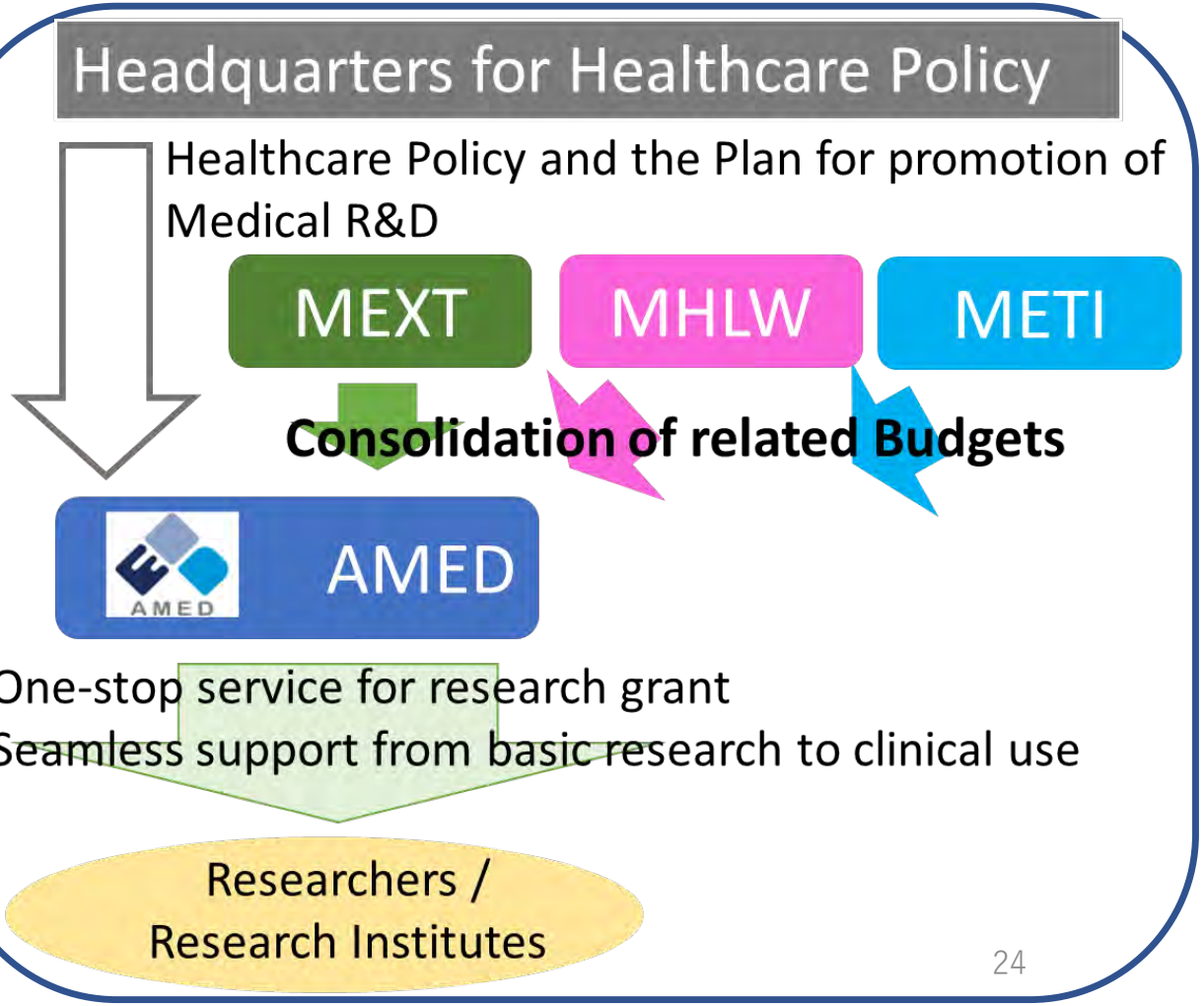

Research Centers for Clinical Applications of iPSCs to Specific Diseases/Organs

Kyoto Univ.
- Parkinson's Disease
- Cartilage Fracture
- Highly functional regenerated CAR-T cell

Keio Univ.
- Spinal Cord Injury
- Organoid and Organ Scaffold

Osaka Univ.
- Heart Disease
- Corneal Disease

Core Center for iPS Cell Research

Center for iPS Cell Research and Application, Kyoto Univ.(CiRA)

The Univ. of Tokyo
- transplantable human organs

Kobe City Eye Hospital
- Retinal Disease

RIKEN
- NKT cells for Cancer Treatment

Yokohama City Univ.
- Hepatic Disease

TMDU
- Inflammatory Bowel Disease

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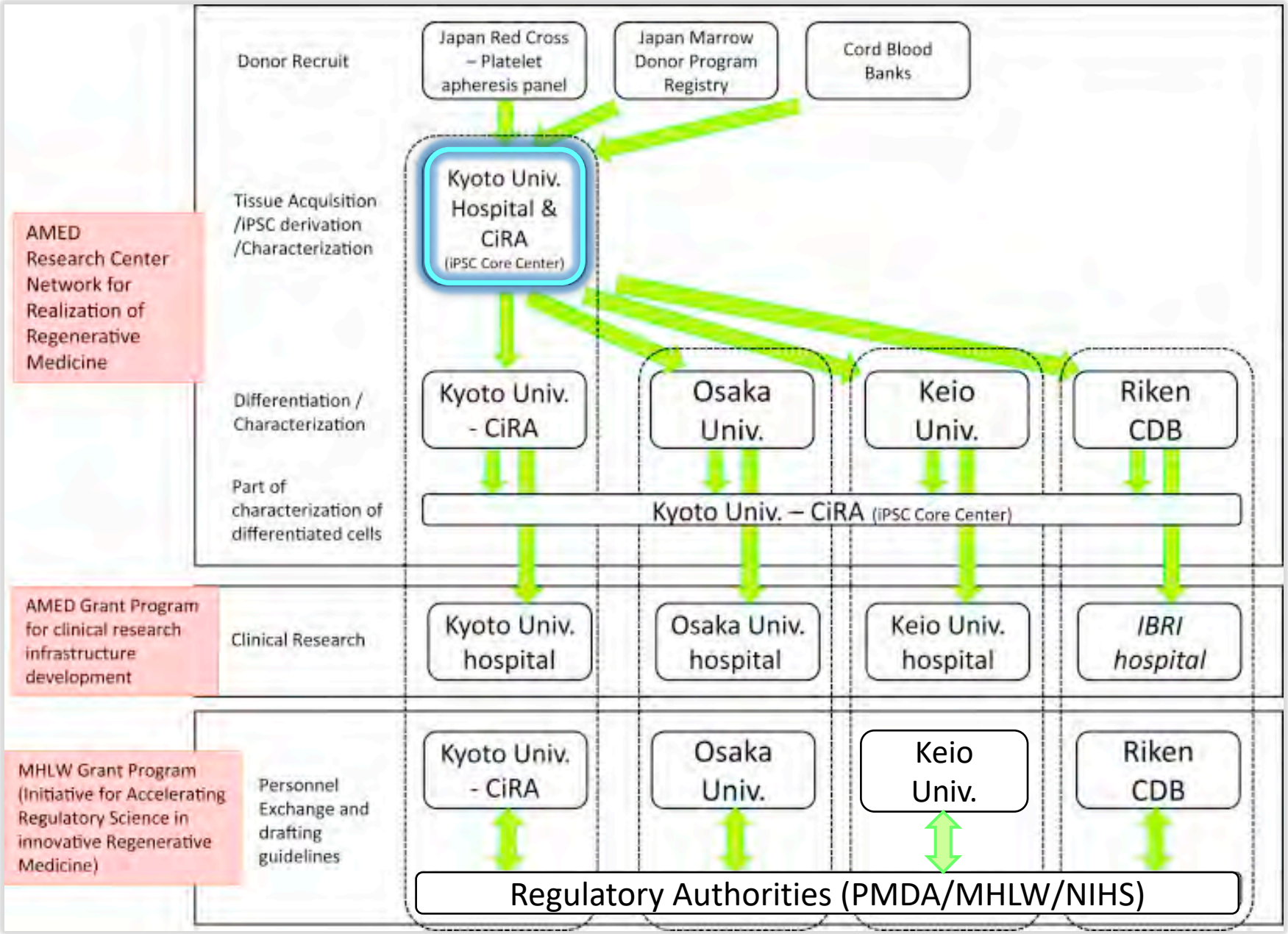
R&D Collaboration between the Major Research Centers and Regulatory Authorities for the Development of iPSC-derived Products



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The Japanese Government is promoting the R&Ds and clinical applications of iPSC-derived products with a view to their commercial distributions **by implementing policies of the relevant ministries for** scientific research and development (**MEXT**), public health and pharmaceutical affairs (**MHLW**), and industrial promotion (**METI**) **on a common platform** (**AMED**), and **by having allogeneic iPSCs as starting/raw materials shared among developers**.

AGENDA

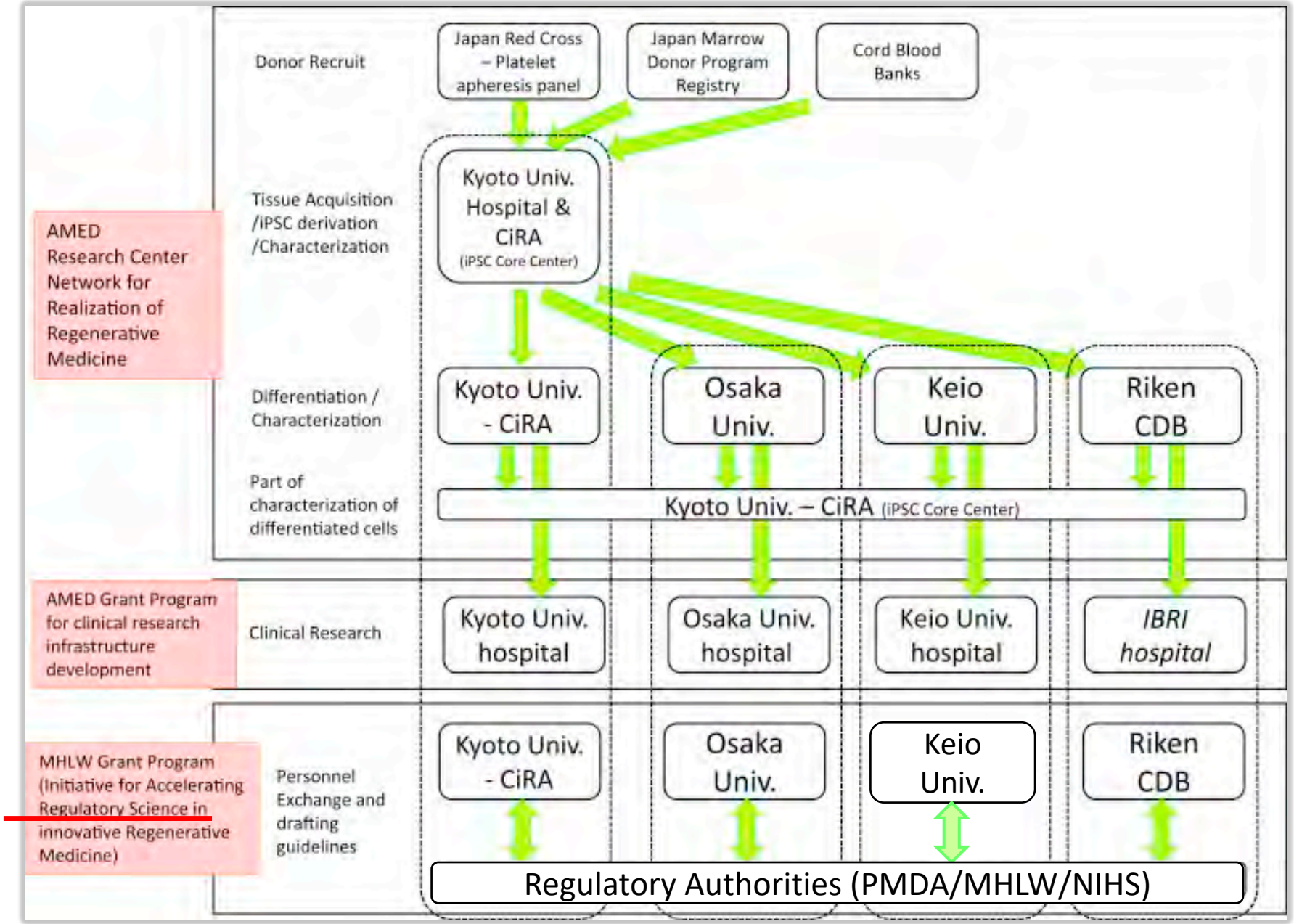
1. Current Status of Clinical Applications of iPSC-derived Products in Japan

2. R&D Support for iPSC-derived Products by Japan Agency for Medical Research & Development (AMED)

3. Regulatory Science on Emerging Safety Issues for iPSC-derived Products

4. NRMD: National Patient Registry System for Clinical Research and Post-Marketing Surveillance on Cell Therapy Products

R&D Collaboration between the Major Research Centers and Regulatory Authorities for the Development of iPSC-derived Products



Modified from Azuma K, Yamanaka S. Regen Ther. 2016;4:36-47. https://www.sciencedirect.com/science/article/pii/S2352320416000134?via%3Dihub

“Regulatory Science”

…is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

https://www.fda.gov/science-research/science-and-research-special-topics/advancing-regulatory-science

Major Challenges in Regulatory Science of Cell Therapy Products

What should be evaluated?

1. Viral safety (allogeneic vs. autologous)
2. Characteristics and eligibility of cells to be used as raw materials
3. Eligibility of ancillary materials of human or animal origin, other than cell substrates
4. Establishment and management of cell banks as cell substrates
5. Manufacturing strategy and process validation to achieve reproducibility of the final product quality
6. Characterization of cells as active ingredients of the final product
7. Identification and specification of critical quality attributes of the final product (QC of the final product)
8. Comparability in the quality of products subject to changes in their manufacturing process/cell banks
9. Design and interpretation of non-clinical safety studies and non-clinical proof-of-concept studies
10. Design and interpretation of tumorigenicity studies (especially for ESC/iPSC-derived products)
11. Immunogenicity of the final product
12. Biodistribution of administered cells *in vivo* and their behavior at the engraftment site
13. Design and interpretation of clinical trials
14. Efficacy and safety follow-up

Safety & eligibility of raw materials

Ensuring the quality of the final product

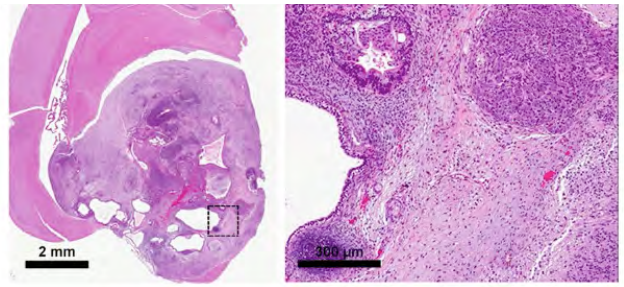
Prediction of safety & efficacy in the non-clinical phase

Clinical Evaluation

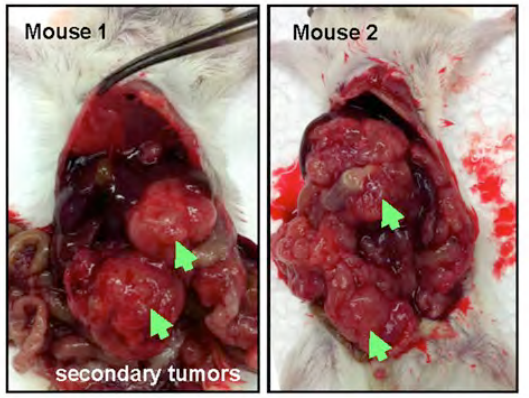
Tumorigenicity

… is one of the major concerns for pluripotent stem cell-derived therapeutic products

- Human pluripotent stem cells (PSC) have the potential to revolutionize regenerative medicine and cell therapy.
- Some clinical trials on pluripotent stem cell-derived products are currently on going, and more trials are expected to start soon in many countries
- However, **cells transformed during the manufacturing process** and **residual undifferentiated PSCs** may form tumors in patients.



Ibon Garitaonandi et al. Scientific Reports | 6:34478

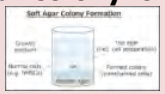


MOUSTAFA M et al. STEM CELLS TRANSLATIONALMEDICINE 2016;5:694–702

Development of Test Methods for Detection of Transformed Cells Intermingled in Cell Therapy Products

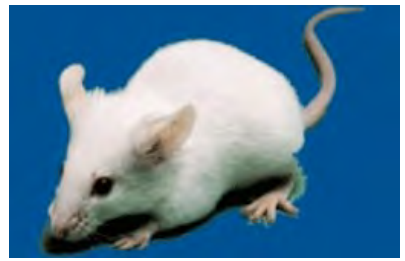
Tumorigenic Cellular Impurities
= A Hazard of PSC-Derived Products

In Vitro Assays

Assays/ Platform	Conventional soft agar colony formation 	Digital soft agar colony formation 	Cell growth analysis 
Positive control	HeLa cells	HeLa cells	HeLa cells
Duration	3 to 4 weeks	3 to 4 weeks	4 weeks or more
Assay principle	Conventional SACF assay based on anchorage-independent cell growth	Image-based screening system for the SACF assay using a high-content cell analyzer	The analysis of cell senescence/growth after serial passaging (compare the growth rates of hMSC w/wo positive controls after 5 passages)
Pros	Low cost	High sensitivity	High sensitivity, Low cost
Cons	Low sensitivity	High cost (needs image scanner)	Time-consuming
Sensitivity	0.02%	0.00001%	0.0001%
Reference	Kusakawa et al., Regen Ther. 2015	Kusakawa et al., Sci Rep. 2015	Kono et al., Biologicals. 2015 Hasebe-Takada et al. Regen Ther 2016

In Vivo Assay

Assays/Platform	Tumorigenicity Test
Animals	NOG mice
Route	Subcutaneous transplantation
Positive control	HeLa cells
Duration	>= 16 weeks
Pros	Direct evaluation in micro environment (expected clinical use site)
Cons	High cost, Long time, Especial facility, Low through put, Histopathological evaluation to confirm malignancy of the tumor
Sensitivity	to detect 10 HeLa cells in 10^6 hMSC (0.0001%) at 17% of probability
Reference	Kusakawa et al., Regen Ther. 2015



Development of Test Methods for Detection of Transformed Cells Intermingled in Cell Therapy Products

Tumorigenic Cellular Impurities
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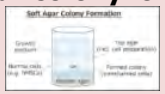
Example 1

In Vitro Assays

Assays/ Platform	Conventional soft agar colony formation 	Digital soft agar colony formation 	Cell growth analysis 
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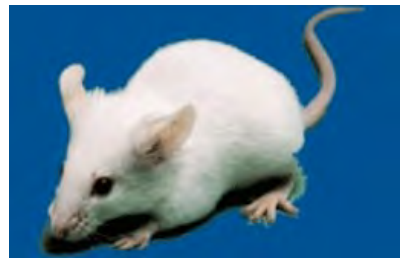
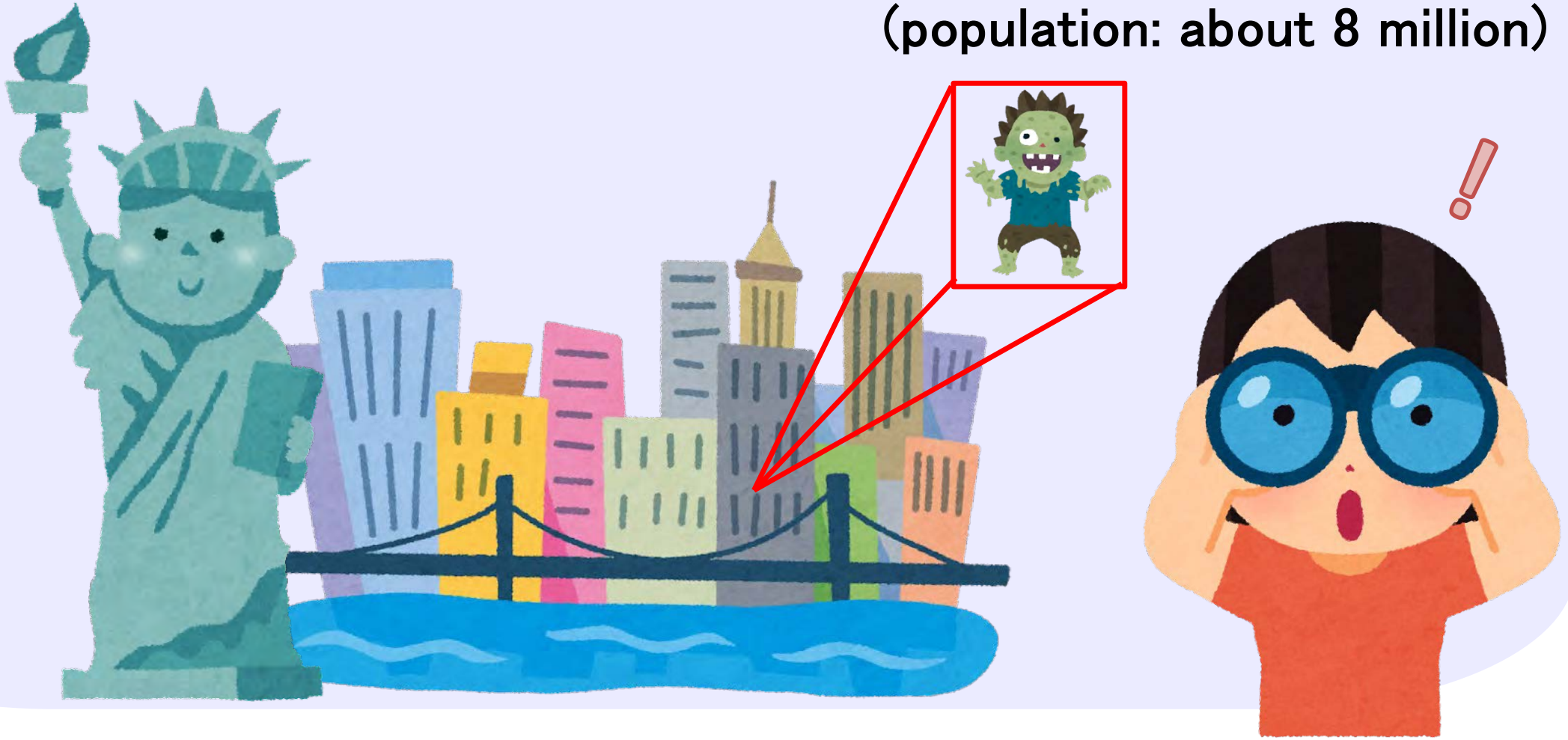


Digital Soft-Agar Colony Formation Assay has achieved the ability to detect cancer cells in normal cells at a ratio of 1 in 10 million

Comparable to the ability to find one zombie in New York City
(population: about 8 million)



Development of Test Methods for Detection of Residual Undiffrentiated PSCs

Tumorigenic Cellular Impurities
= Another Hazard of PSC-Derived Products

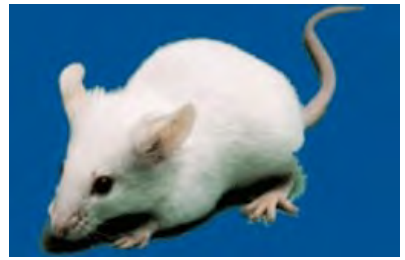
In Vitro Assays

Assays/ Platform	Flow cytometry 	qRT-PCR 	Droplet Digital PCR 	Direct detection using a highly efficient amplification method*
Positive control	iPS cells	iPS cells	iPS cells	iPS cells
Duration	1 day	6 hours	a few hours	about a week
Marker	TRA-1-60 etc	Lin28	Lin28	-
Pros	Simple/quick	Simple/quick, High sensitivity	Simple/quick, High sensitivity	Direct detection, High sensitivity
Cons	Low sensitivity, Indirect detection, Difficulty in the manual selection of marker thresholds	Indirect detection, Lin28 expression is noted in some differentiated cells	Indirect detection, Lin28 expression is noted in some differentiated cells	Time-consuming, Low throughput
Sensitivity	0.1%	0.002%	0.001%	0.01-0.001%
Reference	Kuroda et al., PLoS ONE. 2012	Kuroda et al., PLoS ONE. 2012	Kuroda et al., Regen Ther. 2015	Tano et al., PLoS ONE. 2014

*: eg. cultured on laminin-521 in Essential 8 medium

In Vivo Assay

Assays/Platform	Tumorigenicity Test
Animals	NOG mice
Route	Subcutaneous transplantation
Positive control	iPS cells
Duration	17-30 weeks
Pros	Direct evaluation in micro environment (expected clinical use site)
Cons	High cost, Long time, Especial facility, Low through put, Histopathological evaluation to confirm tumor origin from whether residual undifferentiated iPS cells or transformed cells
Sensitivity	to detect 1000 hiPS cells in $2.5/10^5$ hRPE with 50% probability
Reference	Kanemura et al., Sci Rep. 2013; Kawamata et al., J Clin Med. 2015



Development of Test Methods for Detection of Residual Undiffrentiated PSCs

Tumorigenic Cellular Impurities
= Another Hazard of PSC-Derived Products

Example 2

In Vitro Assays

Assays/ Platform	Flow cytometry 	qRT-PCR 	Droplet Digital PCR 	Direct detection using a highly efficient amplification method*
Positive control	iPS cells	iPS cells	iPS cells	iPS cells
Duration	1 day	6 hours	a few hours	about a week
Marker	TRA-1-60 etc	Lin28	Lin28	-
Pros	Simple/quick	Simple/quick, High sensitivity	Simple/quick, High sensitivity	Direct detection, High sensitivity
Cons	Low sensitivity, Indirect detection, Difficulty in the manual selection of marker thresholds	Indirect detection, Lin28 expression is noted in some differentiated cells	Indirect detection, Lin28 expression is noted in some differentiated cells	Time-consuming, Low throughput
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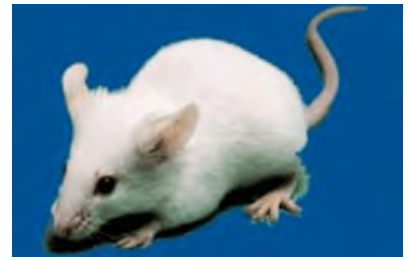


Highly-Efficient Culture Assay

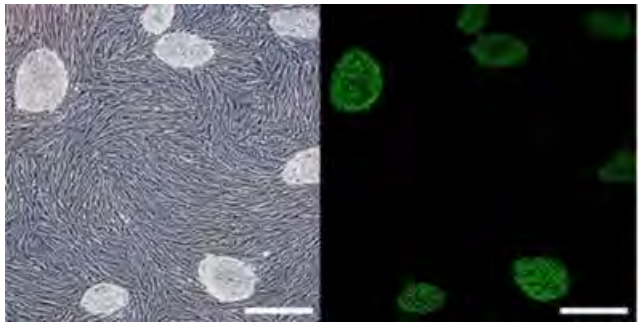
Example 2

detects **residual undifferentiated pluripotent stem cells (PSCs)** in cell therapy products using highly efficient culture system which favors the growth of PSCs

Assays/ Platform	**Highly efficient culture assay**
Positive control	iPS cells *etc*
Duration	about a week
Marker	TRA-1-60 *etc*
Pros	Direct detection, High sensitivity
Cons	Time-consuming, Low throughput
Sensitivity	**1/10,000 - 1/100,000**
Reference	Tano et al., PLoS ONE. 2014 Garitaonandia et al., Scientific Reports. 2016

This assay ...

✓ is able to directly detect a trace amount of undifferentiated PSCs by measuring the number of colonies originated from a single PSC.



Tano et al., PLoS ONE. 2014

✓ is quite sensitive and has a potential to become more sensitive by improving culture system /colony detection method.

Improvement of detection method for residual undifferentiated iPS cells (tumorigenic cells) in differentiated cells derived from human iPS cells

Cytotherapy 23 (2021) 176–183

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journal homepage: www.isct-cytotherapy.org

ELSEVIER

International Society ISCT Cell & Gene Therapy®

FULL-LENGTH ARTICLE

Regulatory Policies

Multisite studies for validation and improvement of a highly efficient culture assay for detection of undifferentiated human pluripotent stem cells intermingled in cell therapy products

Takeshi Watanabe[1,2,*], Satoshi Yasuda[3], Shinji Kusakawa[3], Takuya Kuroda[3], Mayumi Futamura[2,4], Mitsuhide Ogawa[2,5], Hidemi Mochizuki[2,6], Eri Kikkawa[2,7], Hatsue Furukawa[2,8], Masato Nagaoka[2,9], Yoji Sato[3]

[1] Drug Safety Research and Evaluation, Takeda Pharmaceutical Company Limited, Fujisawa, Japan
[2] The Committee for Non-Clinical Safety Evaluation of Pluripotent Stem Cell-Derived Product, Forum for Innovative Regenerative Medicine, Tokyo, Japan
[3] Division of Cell-Based Therapeutic Products, National Institute of Health Sciences, Kawasaki, Japan
[4] Drug Discovery Support Division, Tsukuba Research Institute, BoZo Research Center Inc, Tsukuba, Japan
[5] CMIC Bioresearch Center, CMIC Pharma Science Co, Ltd, Hokuto, Japan
[6] Research Planning Section, Ina Research Inc, Ina-shi, Japan
[7] Research Division, HEALIOS K.K., Kobe, Japan
[8] Integrated & Translational Science, Axcelead Drug Discovery Partners, Inc, Fujisawa, Japan
[9] Life Science Research Laboratory, Tosoh Corporation, Ayase-shi, Japan

Detection of iPS cells in differentiated cells at a ratio of 1 in 5 million (WORLD RECORD!!)

ABSTRACT

Background aims: The Multisite Evaluation Study on Analytical Methods for Non-Clinical Safety Assessment of Human-Derived Regenerative Medical Products (MEASURE) is a Japanese experimental public–private partnership initiative, which aims to standardize methodology for tumorigenicity evaluation of human pluripotent stem cell (hPSC)-derived cell therapy products (CTPs). Undifferentiated hPSCs possess tumorigenic potential, and thus residual undifferentiated hPSCs are one of the major hazards for the risk of tumor formation from hPSC-derived CTPs. Among currently available assays, a highly efficient culture (HEC) assay is reported to be one of the most sensitive for the detection of residual undifferentiated hPSCs.

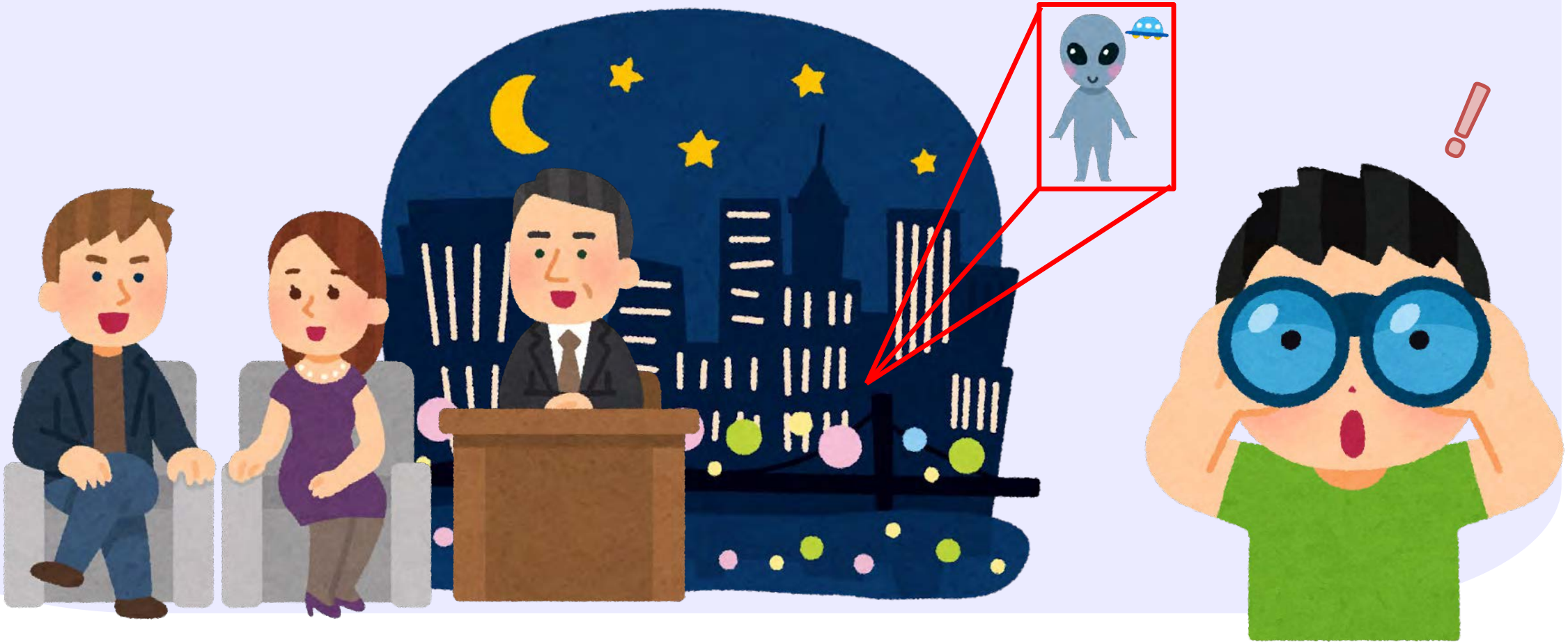
Methods: MEASURE first validated the detection sensitivity of HEC assay and then investigated the feasibility of magnetic-activated cell sorting (MACS) to improve sensitivity.

Results: The multisite experiments confirmed that the lower limit of detection under various conditions to which the human induced pluripotent stem cell lines and culture medium/substrate were subjected was 0.001%. In addition, MACS concentrated cells expressing undifferentiated cell markers and consequently achieved a detection sensitivity of 0.00002%.

Conclusions: These results indicate that HEC assay is highly sensitive and robust and that the application of MACS on this assay is a promising tool for further mitigation of the potential tumorigenicity risk of hPSC-derived CTPs.

Improved Highly-Efficient Culture Assay has achieved the ability to detect residual iPSCs in differentiated cells at a ratio of 1 in 5 million

Comparable to the ability to find one alien in Los Angeles
(population: about 4 million)



"Points to Consider for Detection of Undifferentiated Pluripotent Stem Cells/Transformed Cells, Tumorigenicity Test and Genetic Stability Evaluation of Human Cell-Processed Products“ *[in Japanese]*
(Annex of Notification No. 0627-1 Issued on June 27, 2019, Pharmaceutical and Food Safety Bureau, MHLW)

Table of Contents

Clinical Applications of iPSC/ESC-Derived Products in Japan

in Non-Commercial Clinical Researches under the RM Safety Act and Commercial Clinical Trials under the PMD ACT

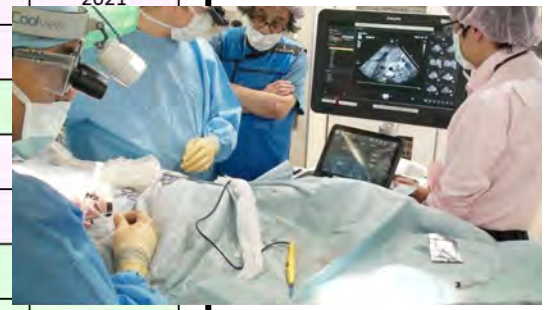
As of October 21, 2023; ** According to a newspaper report

Final Product	Starting Cells	Target Disease	Institution(s)	Type of Clinical Trial	IMP Approval	FIH Trial
Retinal pigment epithelial cells	*Autologous iPSCs*	Exudative age-related macular degeneration	FBRI, RIKEN	Non-commercial clinical research under the RM Safety Act	2013	2014
pigment epithelial cells	Allogeneic iPSCs	Exudative age-related macular degeneration	Kobe City Medical Center, Osaka Univ., Kyoto Univ., RIKEN	Non-commercial clinical research under the RM Safety Act	2017	
paminergic neural progenitor cells	Allogeneic iPSCs	Parkinson's disease	Kyoto Univ.	Clinical trial under the PMD Act	2018	
Platelets	*Autologous iPSCs*	Aplastic anemia	Kyoto Univ.	Non-commercial clinical research under the RM Safety Act	2018	
neal epithelial cells	Allogeneic iPSCs	Corneal epithelial stem cell exhaustion	Osaka Univ.	Non-commercial clinical research under the RM Safety Act	2019	
Hepatocytes	*ESCs (Allogeneic)*	Congenital urea cycle disorder	NCCHD	Clinical trial under the PMD Act	2019	
Cardiomyocytes	Allogeneic iPSCs	Ischemic cardiomyopathy	Osaka Univ.	Clinical trial under the PMD Act	2019	
Neural progenitor cells	Allogeneic iPSCs	Subacute spinal cord injury	Keio Univ. etc.	Non-commercial clinical research under the RM Safety Act	2019	2021
Retinal photoreceptor cells	Allogeneic iPSCs	Retinitis pigmentosa	Kobe City Eye Hospital	Non-commercial clinical research under the RM Safety Act	2020	
NKT cells	Allogeneic iPSCs	Recurrent or advanced head and neck cancer	Chiba Univ., RIKEN	Clinical trial under the PMD Act	2020	
Cartilage	Allogeneic iPSCs	Knee articular cartilage injury	Kyoto Univ.	Non-commercial clinical research under the RM Safety Act	2020	
pigment epithelial cells	Allogeneic iPSCs	Retinal pigment epithelial insufficiency	Kobe City Eye Hospital	Non-commercial clinical research under the RM Safety Act	2021	
ymphoid Cells/NK cells pressing GPC3-CAR	Allogeneic iPSCs	Ovarian cancer	Kyoto Univ., NCRI	Clinical trial under the PMD Act	2021	
Platelets	Allogeneic iPSCs	Thrombocytopenia	Megakaryon, Kyoto Univ., CiRA-F	Clinical trial under the PMD Act	2021	2022
eal endothelial cells	Allogeneic iPSCs	Bullous keratopathy	Keio Univ.	Non-commercial clinical research under the RM Safety Act	2021	2023
Cardiomyocytes	Allogeneic iPSCs	Ischemic Cardiomyopathy	Heartseed, Novo Nordisk	Clinical trial under the PMD Act	2021	2023

https://nd.natureasia.com/figure/4438/56992/phone/1

https://english.kyodonews.net/news/2020/01/47a1ba1f19f1-japan-researchers-conduct-worlds-1st-transplant-of-ips-heart-muscles.html

https://japan-forward.com/osaka-university-team-does-worlds-first-successful-ips-cell-derived-corneal-transplant/



https://www.sankei.com/article/20200521-B5I5HI55EBI6XMQ5AVIKYLXQVY/photo/UDRYD4AHVFJPDHGFB54X2ZSB2Q/

Regulatory science research has contributed to clinical applications of PSC-derived products through the development of test methods for the assessment of their quality and safety.

In Japan, regulatory science researches have been conducted under the policy of promoting the development of new therapeutic products using iPS cells, and various test methods have been developed for new safety issues such as tumorigenicity.

Through validation by domestic and international collaborative efforts of stakeholders, these test methods are expected to be utilized as tools to efficiently deliver new iPS cell-derived products to patients around the world who are waiting for a cure.

3. Regulatory Science on Emerging Safety Issues for iPSC-derived Products

4. NRMD: National Patient Registry System for Clinical Research and Post-Marketing Surveillance on Cell Therapy Products

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https://www.youtube.com/watch?v=LVCLVkPzrNQ

Introduction of NRMD

Thank you for your attention!

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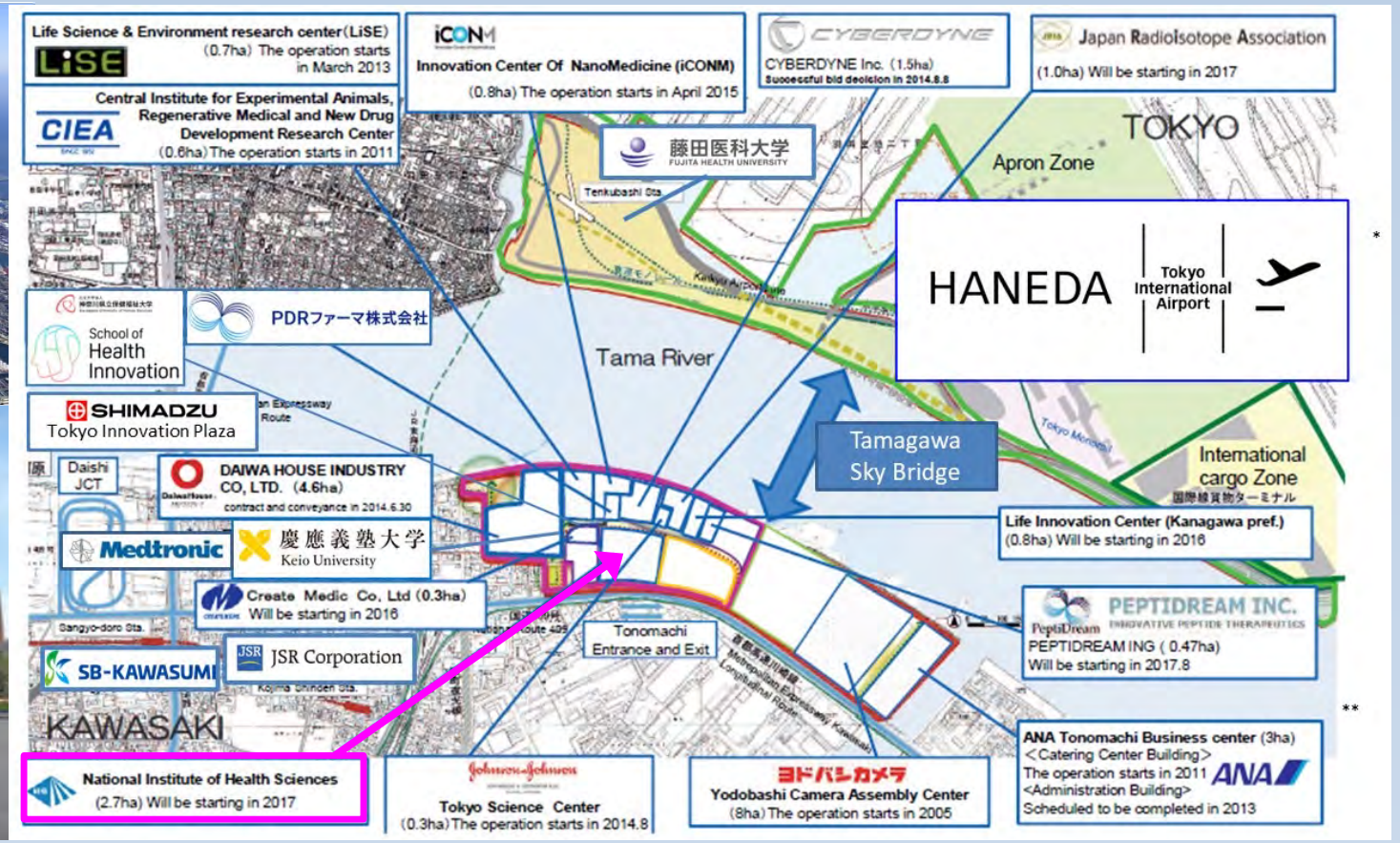
E-mail: yoji@nihs.go.jp



* https://www.oag.com/hubfs/air-canada-787.jpg

** http://www.city.kawasaki.jp/en/page/0000038680.html