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Virtual Conference

The 4th Asia Partnership Conference of Regenerative Medicine Associations

Recent Regulatory Developments in Japan for Ensuring the Quality and Safety of Cell-Based Therapeutic Products

Yoji SATO, PhD

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AGENDA

1. MCP: the Minimum Consensus Package for Ensuring the Quality and Safety of Cell Therapy Products

2. A Points-to-Consider Document Regarding Tumorigenicity Assessment of Cell Therapy Products

3. Drafting a Guidance Document on Comparability Evaluation Before & After Changes in Manufacturing Process of Cell Therapy Products

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Q/S Guidelines for Cell-Based Therapeutic Products

Good Tissue Practice (GTP) Guidelines

General Principles for the Handling and Use of Cell/Tissue-Based Products
PFSB/MHLW Notification No.1314 (2000) Appendix1;
No 0330030 (Revision, 2007)

Standards for Biological Raw Materials
(also translated as "Standards for Biological Ingredients")
MHLW Ministerial Notice No. 210. (2003);
No. 37. (Revision, 2018)

Good Cell, gene and Tissue-Based Prod. Mfg. Practice (GCTP)

Ministerial Ordinance on Good Practices in Manufacturing Control and Quality Control of Regenerative Medical Products
MHLW Ministerial Ordinance No. 93（2014）

Standards for Manufacturing Facility

Regulations for Buildings and Equipment of Pharmacies
MHLW Ministerial Ordinance No.2(1961);
No.87 (Revision, 2014)

Technical Guidelines Separately Written for Each Type of Starting Cell Materials

Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of
Allogeneic Human Cell/Tissue
PFSB/MHLW Notifications No. 0912006 (2008)

Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of
Autologous Human Cell/Tissue
PFSB/MHLW Notifications No.0208003 (2008)

Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of
Allogeneic Human Somatic Stem Cells
PFSB/MHLW Notifications No.0907-3（2012）

Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of
Autologous Human Somatic Stem Cells
PFSB/MHLW Notifications No.0907-2（2012）

Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of
Allogeneic Human iPS(-like) Cells
PFSB/MHLW Notifications No.0907-5（2012）

Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of
Autologous Human iPS(-like) Cells
PFSB/MHLW Notifications No.0907-4（2012）

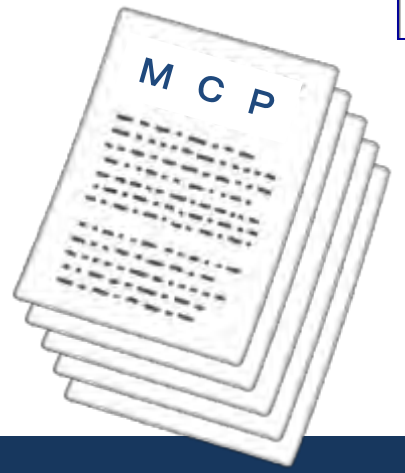
Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of
Allogeneic Human ES Cells
PFSB/MHLW Notifications No.0907-6（2012）

(…and some monographs for specific products are also available.)

Guidelines on Ensuring Quality and Safety of Products Derived by Processing of Human Cells/Tissues

- Describe the basic technical elements to ensure the quality and safety of therapeutic products derived from processing of autologous and allogeneic human (stem) cells

- Clarify differences with respect to data requirements and evaluation between MA application and application of a clinical trial for an investigational new product. For the latter, points to consider are mentioned to make sure if there are any quality and safety concerns that might pose an obstacle to initiate a clinical trial.



“Minimum Consensus Package (MCP) for Ensuring the Quality and Safety of Cell Therapy Products”

Guidance for Users of the Seven GL Documents

Written by the Original Drafting Group of the GLs

The MCP Drafting Group

Co-chairs

Takao Hayakawa	(Osaka Univ./ NIHS)
Yoji Sato	(NIHS)

Members

Takashi Aoi	(Kobe Univ.)
Akihiro Umezawa	(NCCHD)
Kiyoshi Okada	(Osaka Univ.)
Keiya Ozawa	(Jichi Medical Univ.)
Kazuhiro Takekita	(Osaka Univ./ Hyperion Drug Discovery)
Akifumi Matsuyama	(Osaka Habikino Medical Center)
Satoshi Yasuda	(NIHS)
Masayuki Yamato	(Tokyo Women's Medical Univ.)

Observers

Division of Regenerative Medicine Research, AMED
Research and Policy Division, MHLW
Medical Device Evaluation Division, MHLW
Office of Cellular and Tissue-based Products, PMDA

Necessary and Sufficient Items to Ensure Quality & Safety

- In R&D and review process of an individual cellular or gene therapy product, in order to accurately and rationally ensure the quality and safety, appropriate tests and data interpretations should be conducted, based on the risk of the product, which is assessed according to the type, characteristics and clinical application of the product. Excessive tests and data should not be required.

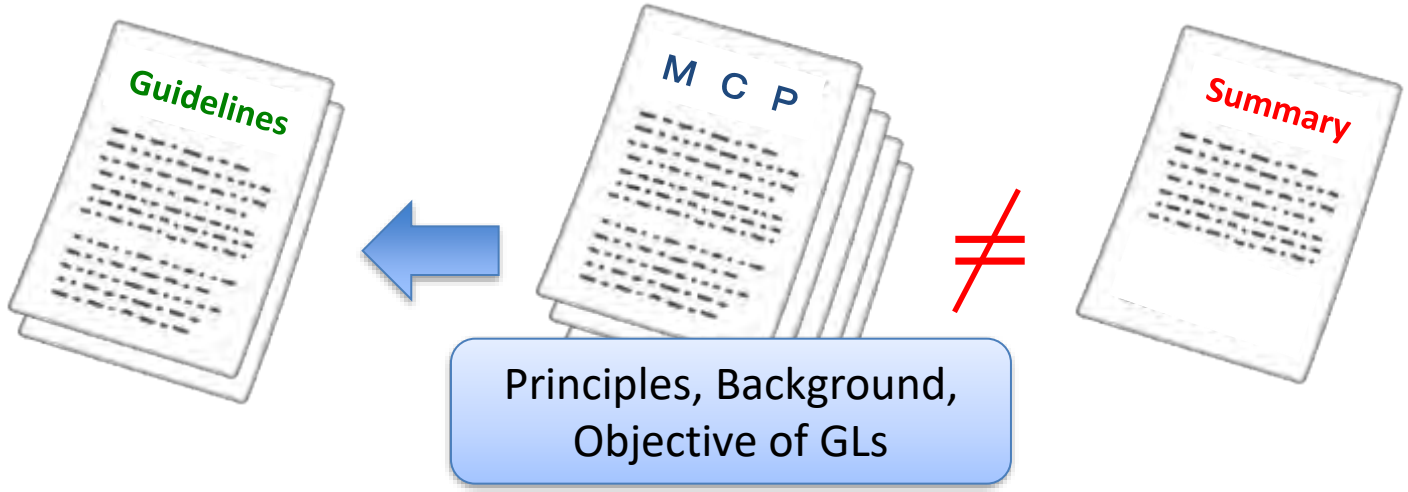
- However, to ensure the quality, safety, etc., of individual products, it is not easy for the developers themselves to select necessary and efficient matters and to evaluate the data among comprehensive matters indicated in the current guidelines. This issue has become a bottleneck for development.

For more reasonable, efficient, and effective product development, it is useful to share technical elements and basic concepts (minimum consensus package [MCP]), which will be common bases for anticipated most human cell-based products, among the stakeholders.

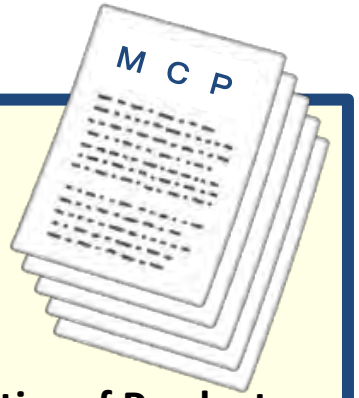
Minimum Consensus Package (MCP) for Ensuring the Quality and Safety of CTPs

- Basic technical requirements, concepts and principles that are common to most of cell therapy products

  … Aiming to **prevent a divergence of GLs' interpretation and operation (unreasonable / excessive requirements)**, by sharing the minimum necessary recognition (principle, background, objective, etc.)



Minimum Consensus Package (MCP) for Ensuring the Quality and Safety of CTPs



CONTENTS

39 Pages!

Hayakawa T, Sato Y *et al.,* 再生医療（SAISEI-IRYO）2020;**19:**409-448 [in Japanese (English version coming soon?)]

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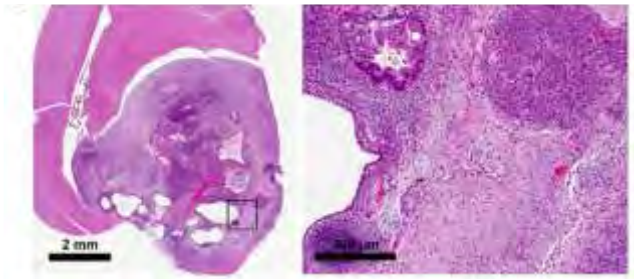
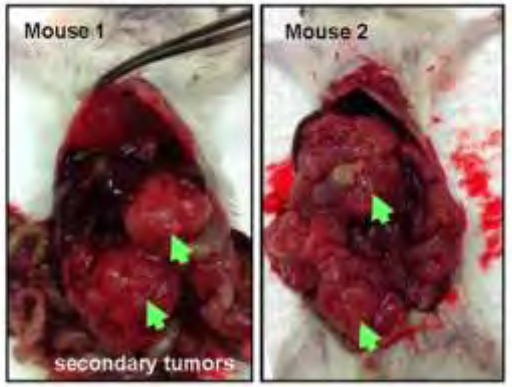
Tumorigenicity

… is one of the major concerns for PSC-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

Documents suggesting the need for tumorigenicity assessment of CTPs

- U.S. Food and Drug Administration, Cellular & Gene Therapy Guidances
- European Medicines Agency, Guidelines for advanced therapy medicinal products
- Japanese guideline documents for ensuring the quality and safety of regenerative medical products derived from the processin
- U.S. Food and Drug … from Human Embryonic Stem Ce …
- EMA/CAT/571134/… cell-based medicinal products
- Japan Ministry of Health, Labour and Welfare/Notification 0613-3/2016, Points for certified special committees for regenerative medicine to consider when evaluating tumorigenicity assessment in provision plans of regenerative medicine using human pluripotent stem cells

… do not describe detailed characteristics and protocols of test methods

Purposes of test methods for the assessment of tumorigenicity of CTPs

1. Detection or quantitation of tumorigenic cells

= Quality control of intermediate/finished products during manufacturing processes

Safety-Related Quality Testing

- The amount of **tumorigenic cellular impurities** is one of critical quality attributes.
  a. Maliganant transformed cells
  b. Residual ES/iPS cells

- They could be evaluated by

  ***in vitro* methods, e.g. soft-agar colony formation assay, qRT-PCR for pluripotency markers**

  (or *in vivo* tumorigenicity testing with immunodeficient animals)

---

2. Non-clinical safety assessment of finished products

Non-clinical Safety Testing

- For estimation of tumorigenicity of CTP **at the site of engraftment**
- cannot be evaluated by any other methods than

  ***in vivo* tumorigenicity testing with immunodeficient animals**

Methods for Detection of Transformed/Immortalized Cells

Assay	*In vivo* tumorigenicity testing using NOG mice and Matrigel	Soft agar colony formation assay	Digital soft agar colony formation assay	Cell Growth Analysis
Purpose	Detection of tumorigenic cellular impurities	Detection of anchorage-independent growth (malignant transformed cells)	Detection of anchorage-independent growth (malignant transformed cells)	Detection of immortalized cells (transformed cells)
Time	>= 16 weeks	3-4 weeks	3-4 weeks	4 weeks or more
Advantage	◆Direct ◆Analyzes tumor formation in a specific microenvironment →non-clinical safety assessment	◆Inexpensive ◆More rapid compared with in vivo testing ◆Isolates and characterizes malignant transformed cells	◆More rapid compared with in vivo testing ◆Isolates and characterizes malignant transformed cells	◆Simple ◆Inexpensive ◆Detects both benign and malignant transformed cells
Disadvantage	◆Costly & Time-consuming ◆Needs a clean animal facility ◆Unable to detect benign transformed cells	◆Indirect ◆Not applicable to floating cells (blood cells) ◆Unable to detect benign transformed cells and human ES/iPS cells	◆Indirect ◆Not applicable to floating cells (blood cells) ◆Unable to detect benign transformed cells and human ES/iPS cells	◆Indirect ◆Takes time to detect trace amount of immortalized cellular impurities
Limit of detection	HeLa cells mixed in hMSCs at a ratio of 1/1E+6 (0.0001%) at a probability of 17%	HeLa cells mixed in hMSCs at a ratio of 1/1E+3 (0.1%) (calculated LOD: 0.02%)	HeLa cells mixed in hMSCs at a ratio of 1/1E+7 (0.0001%)	HeLa cells mixed in hMSCs at a ratio of 1/1E+6 (0.0001%), Immortalized hMSCs in hMSCs at a ratio of 1/E+5 (0.001%)
Reference	Kusakawa *et al.*, *Regen Ther.* 2015	Kusakawa *et al.*, *Regen Ther.* 2015	Kusakawa *et al.*, *Sci Rep.* 2015	Kono *et al., Biologicals.* 2015 Hasebe-Takada et al., *Regen Ther.* 2016

Methods for Detection of Residual hPSCs

Assay	*In vivo* tumorigenicity test using NOG mice	Flow cytometry	GlycoStem-HP Method
Purpose	Detection of tumorigenic cells	Detection of undifferentiated/pluripotent cells	Detection of undifferentiated/pluripotent cells
Time	17-30weeks	1 day	=< 3 hours
Advantage	◆Direct ◆Analyzes tumor formation in a specific microenvironment	◆Rapid ◆Analyzes individual cells	◆Nondestructive ◆Simple ◆High throughput
Dis-advantage	◆Costly & Time-consuming ◆Specific Animal Facility	◆Indirect ◆Detects only the cells that express the known marker proteins ◆Gating techniques strongly influence the results	◆Indirect ◆Unable to detect the expression level of the marker in individual cells ◆Culture media influence the results
Limit of detection	1000 iPSCs in 2.5E+5 hRPEs（0.4%）	0.1% of hiPSCs in hRPEs (TRA-1-60)	0.05% of hiPSCs in HEK293T cells (H3+ podocalyxin)
Reference	Kanemura *et al., Sci Rep.* 2013 Kawamata *et al., J Clin Med.* 2015	Kuroda *et al., PLoS ONE.* 2012	Tateno et al., *Sci Rep.* 2014

Assay	qRT-PCR	Droplet Digital PCR	Highly Efficient Culture of PSCs using Essential-8/LN521
Purpose	Detection of undifferentiated/pluripotent cells	Detection of undifferentiated/pluripotent cells	Detection of hPSCs
Time	Approx. 6 hours	Approx. 6 hours	About a week
Advantage	◆Rapid ◆Simple ◆Quantitative ◆Highly sensitive	◆Rapid ◆Simple ◆Quantitative ◆Highly sensitive	◆Direct ◆Easy ◆Analyzes residual hPSCs
Dis-advantage	◆Indirect ◆Detects only the cells that express the known marker genes	◆Indirect ◆Detects only the cells that express the known marker genes	◆Time-consuming
Limit of detection	Approx. 0.002% of hiPSCs in hRPEs (*LIN28*)	0.001% of hiPSCs in human cardiomyocytes (*LIN28*)	0.01-0.001% of hiPSCs in hMSCs
Reference	Kuroda *et al., PLoS ONE.* 2012	Kuroda *et al., Regen Ther.* 2015	Tano et al., *PLoS ONE.* 2014

Points to consider for *in vivo* test methods

- Selection of test animals
- Control cell selection, detection capability of the test system
- Number of test animals
- Administration site of the test sample
- Number of cells in the sample, and the form of the sample
- Duration of observation
- Observation of the administration site
- Histological evaluation of the administration site, identification of human cells administered and the confirmation of engraftment, histological evaluation of the degree of differentiation
- Interpretation of results

“Points to Consider Regarding Tests to Detect Undifferentiated Pluripotent Stem Cells/Transformed Cells in Human Cell-based Products, Tumorigenicity Studies and Genomic Stability Evaluation” (MDED/PSEHB/MHLW Notification 0627-1, June 27, 2019)

Out of references and points to consider regarding nonclinical evaluation of the quality/safety of human cell-based products, this document provides representative examples of tests that can be used to detect undifferentiated pluripotent stem cells and transformed cells mixed in human cell-based products as well as points to consider in selecting tests from these options to evaluate the quality/safety of specific human cell-based products.

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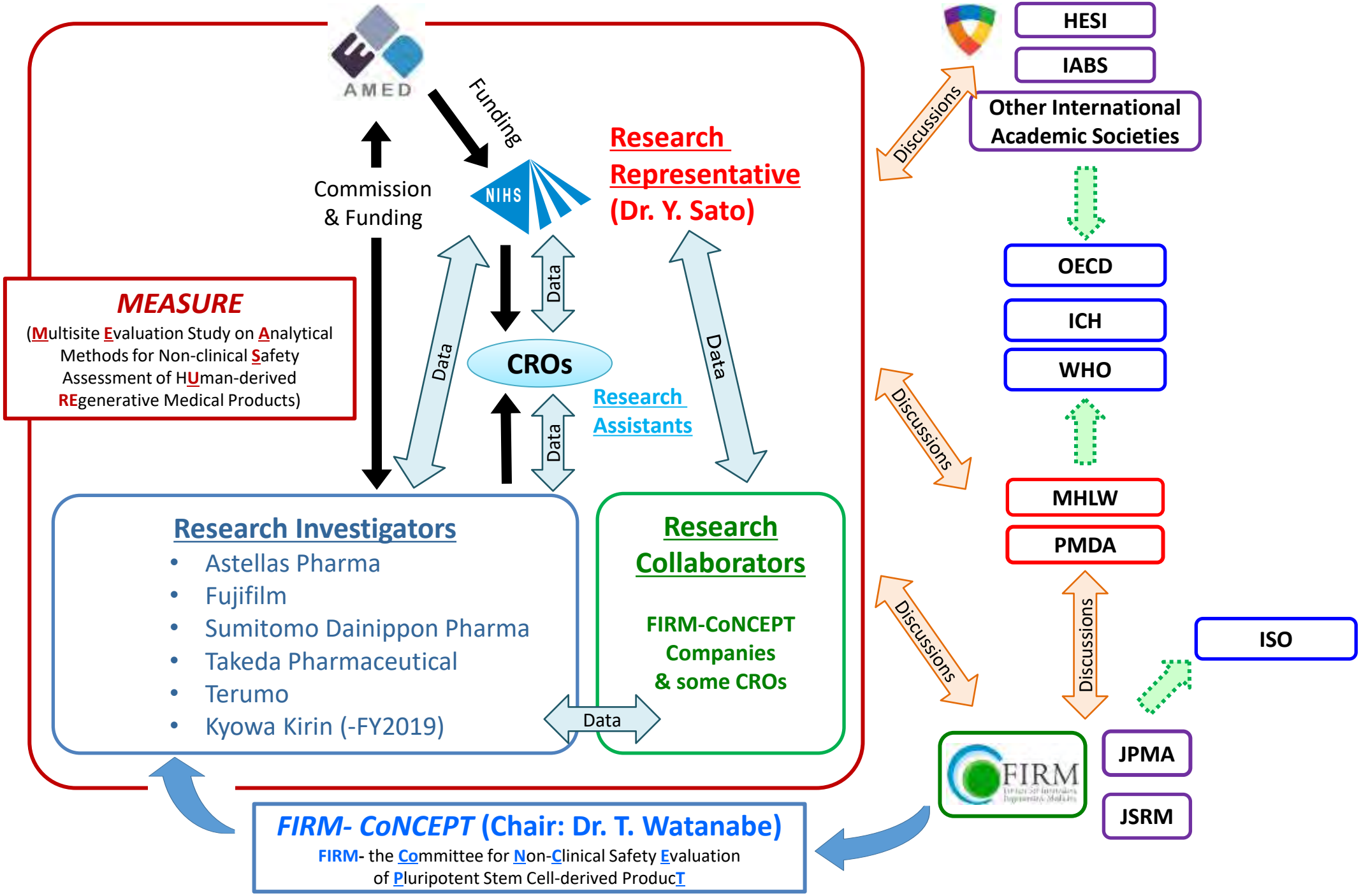
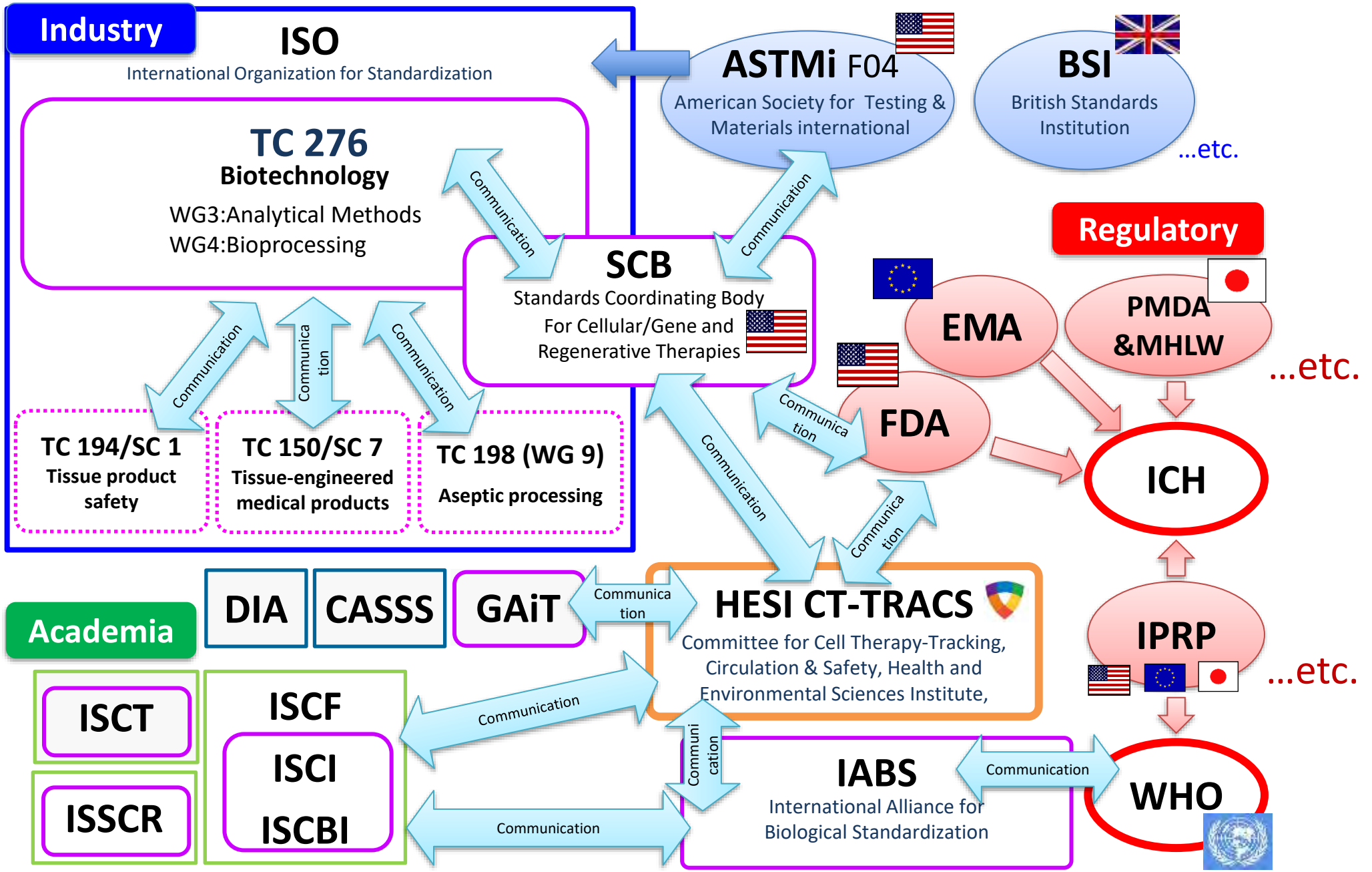

AMED
Funding
Commission
& Funding
NIHS
Research
Representative
(Dr. Y. Sato)
MEASURE
(Multisite Evaluation Study on Analytical Methods for Non-clinical Safety Assessment of HUman-derived REgenerative Medical Products)
Data
Data
Data
Data
CROs
Research
Assistants
Research Investigators
• Astellas Pharma
• Fujifilm
• Sumitomo Dainippon Pharma
• Takeda Pharmaceutical
• Terumo
• Kyowa Kirin (-FY2019)
Research
Collaborators
FIRM-CoNCEPT
Companies
& some CROs
Data
FIRM- CoNCEPT (Chair: Dr. T. Watanabe)
FIRM- the Committee for Non-Clinical Safety Evaluation of Pluripotent Stem Cell-derived ProducT
HESI
IABS
Other International Academic Societies
Discussions
OECD
ICH
WHO
Discussions
MHLW
PMDA
Discussions
Discussions
ISO
FIRM
JPMA
JSRM

International Platforms for Scientific Discussions on Regulatory Harmonization and Standardization of Cell Therapy Products



Recent Publication by
HESI Committee of Cell Therapy-TRAcking, Circulation & Safety (CT-TRACS)

Cytotherapy. 2019;21:1095-1111

HESI

International Society ISCT Cell & Gene Therapy

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REVIEW

Tumorigenicity assessment of cell therapy products: The need for global consensus and points to consider

Y. SATO[1], H. BANDO[2,*], M. DI PIAZZA[3], G. GOWING[4], C. HERBERTS[5,†], S. JACKMAN[6], G. LEONI[7], S. LIBERTINI[8], T. MACLACHLAN[9], J.W. MCBLANE[10], L. PEREIRA MOURIÈS[11], M. SHARPE[7], W. SHINGLETON[12,‡], B. SURMACZ-CORDLE[7], K. YAMAMOTO[13] & J.W. VAN DER LAAN[5,*]

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Chair of SWP/CHMP/EMA

Abstract

Pluripotent stem cells offer the potential for an unlimited source for cell therapy products. However, there is concern regarding the tumorigenicity of these products in humans, mainly due to the possible unintended contamination of undifferentiated cells or transformed cells. Because of the complex nature of these new therapies and the lack of a globally accepted consensus on the strategy for tumorigenicity evaluation, a case-by-case approach is recommended for the risk assessment of each cell therapy product. In general, therapeutic products need to be qualified using available technologies, which ideally should be fully validated. In such circumstances, the developers of cell therapy products may have conducted various tumorigenicity tests and consulted with regulators in respective countries. Here, we critically review currently available *in vivo* and *in vitro* testing methods for tumorigenicity evaluation against expectations in international regulatory guidelines. We discuss the value of those approaches, in particular the limitations of *in vivo* methods, and comment on challenges and future directions. In addition, we note the need for an internationally harmonized procedure for tumorigenicity assessment of cell therapy products from both regulatory and technological perspectives.

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Basic Approach for Evaluation of Comparability Before and After Manufacturing Process Changes (= ICH Q5E)

1. Attempt to assess and assure the comparability, based on the analysis results of quality attributes of the product before and after the process change.

2. When the quality attributes of the product before and after the manufacturing process change appear to be changed, and the comparability cannot be fully explained, due to reasons such as the relationship between the quality attributes and safety/efficacy not being fully understood, consider the comparability assessment with the results of non-clinical or clinical trials.

Comparability of Cell & Gene Therapy Products

Regen. Med. (2016) 11(5), 483–492

White Paper

Regenerative Medicine

Comparability: manufacturing, characterization and controls, report of a UK Regenerative Medicine Platform Pluripotent Stem Cell Platform Workshop, Trinity Hall, Cambridge, 14–15 September 2015

This paper summarizes the proceedings of a workshop held at Trinity Hall, Cambridge to discuss comparability and includes additional information and references to related information added subsequently to the workshop. Comparability is the need to demonstrate equivalence of product after a process change, a recent publication states that this 'may be difficult for cell-based medicinal products'. Therefore a well-managed change process is required which needs access to good science and regulatory advice and developers are encouraged to seek help early. The workshop shared current thinking and best practice and allowed the definition of key research questions. The intent of this report is to summarize the key issues and the consensus reached on each of these by the expert delegates.

First draft submitted: 10 May 2016; Accepted for publication: 17 May 2016; Published online: 12 July 2016

Keywords: advice • comparability • human pluripotent stem cell derived • manufacturing • quality • regulatory

David J Williams[1], Richard Archer, Peter Archibald, Ioannis Bantounas, Ricardo Baptista, Roger Barker, Jacqueline Barry, Florence Bietrix, Nicholas Blair, Julian Braybrook, Jonathan Campbell, Maurice Canham, Amit Chandra, Gabor Foldes, Rudy Gilmanshin, Mathilde Girard, Erwin Goosjes, Zoe Hewitt, Paul Hound, Johan Hyllner, Helen Jesson, Jasmin Kay, Julie Kerby, Nina Kotsopoulou, Stanley Kowalski, Chris Leider, Damian Marshall, Louis Masi, Mark McCall, Conor McCann, Nicholas Medcalf, Harry Moore, Hiroki Ozawa, David Pan, Malin Parmar, Anne L Plant, Yvonne Reinwald, Sujith Sebastian, Glyn Stacey, Robert J Thomas, Dave Thomas, Jamie Thurman-Newell, Marc Turner, Loriana Vitillo, Ivan Wall, Alison Wilson, Jacqueline Wolfrum, Ying Yang & Heiko Zimmerman

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 December 2019
EMA/CAT/499821/2019
Committee for Advanced Therapies (CAT)

Questions and answers

Comparability considerations for Advanced Therapy Medicinal Products (ATMP)

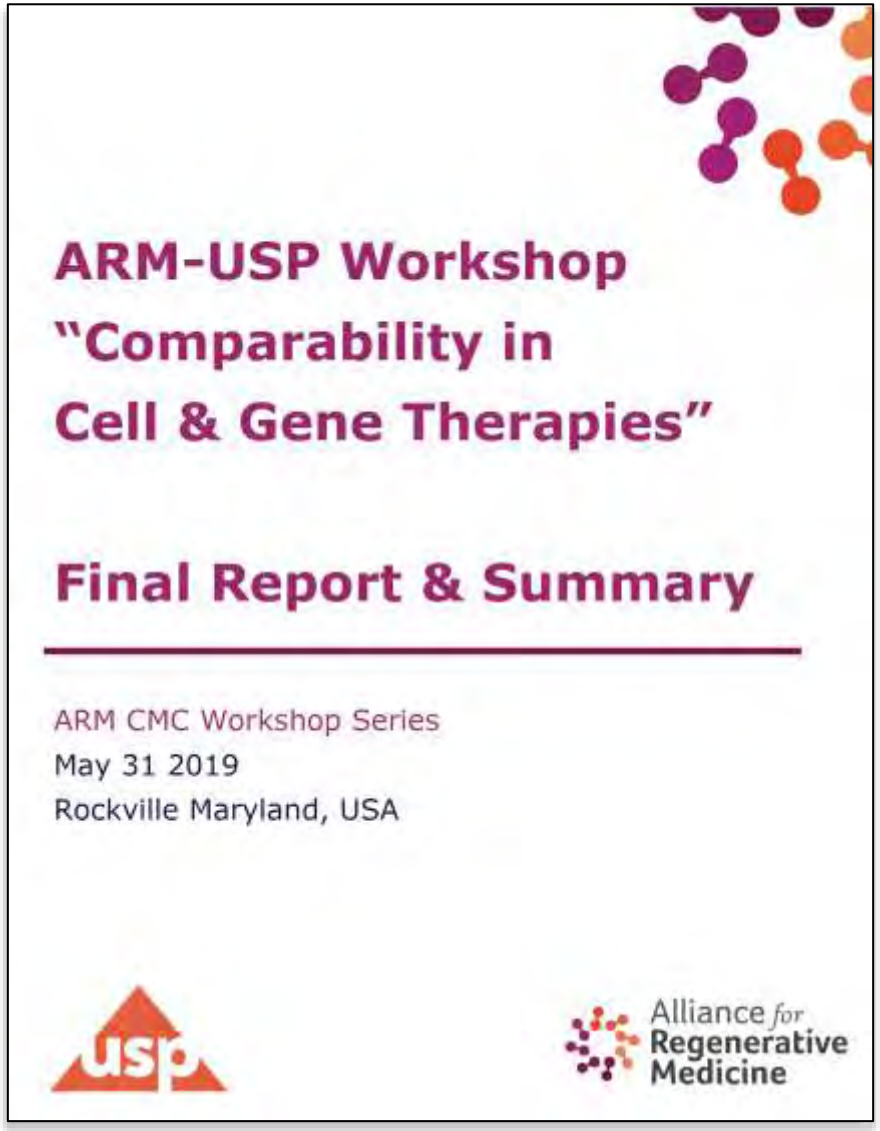
Introduction

CHMP scientific advice questions are often related to the suitability of comparability proposals following changes to ATMP manufacturing processes or due to introduction of additional manufacturing sites. Manufacturing process changes may encompass improvements/change in equipment, raw materials and critical starting materials such as the cells or the vector or their suppliers, manufacturing process scale or product stability. Such changes are frequent, especially in the early stages of development of ATMPs.

Every change in manufacture should be done in accordance with GMP. The criticality of the changes and the estimation of their impact on the characteristics of the product should determine the amount of comparability data needed. Where applicable, the Variation Regulation[1] (for authorised ATMPs) or the clinical trial framework (for investigational ATMPs) should be followed.

A suitable comparability program is required to support the introduction of changes during the development stages of an ATMP. The acceptable level of flexibility is progressively reduced from the non-clinical stage to the pivotal clinical use. Comparability is also an important tool to support changes after marketing authorisation where the process and the product are expected to be well defined and appropriately controlled by quality specifications and characterisation tools.

Comparability of Cell & Gene Therapy Products



Morning Session 1 – Industry & Regulatory Perspectives:

Presenters (slides available at end of report):

Dr. Zenobia Taraporewala (CMC Reviewer and Acting GT Team Lead, CBER, FDA)

Dr. Margarida Menezes-Ferreira (Sr. Assessor Infarmed, Member of CAT, EMA)

Fouad Atouf (VP Global Biologics, USP)

Michael Lehmicke (Dir. Science & Industry Affairs, ARM)

Morning Session 2 – Group Thought Exercises:

Session Leaders:

Keith Wannacott, Pfizer

Mike Lehmicke, ARM

Natalie Ward, C&GT Catapult

Adam Roose, ARM

Jim Richardson, USP

Afternoon Session 1 – Breakout Discussions:

Session Leaders:

Nimi Chhina, BioMarin

Dan Leblanc, Flexion Therapeutics

Kanti Thirumoothry, Kite Pharma

Steve Rabin, Iovance Biotherapeutics

Dawn Henke, Standards Coordinating Body

Rebecca Potts, USP

Comparability of Cell Therapy Products

Study on Comparability of the Quality of Cell Therapy Products Subject to Changes in Their Manufacturing Process (FY2019-2021)

[Goal]

Development of a draft guideline document intended to advise what data and information should be collected to demonstrate that manufacturing process changes do not have a detrimental effect on the quality, safety and efficacy of cell therapy products

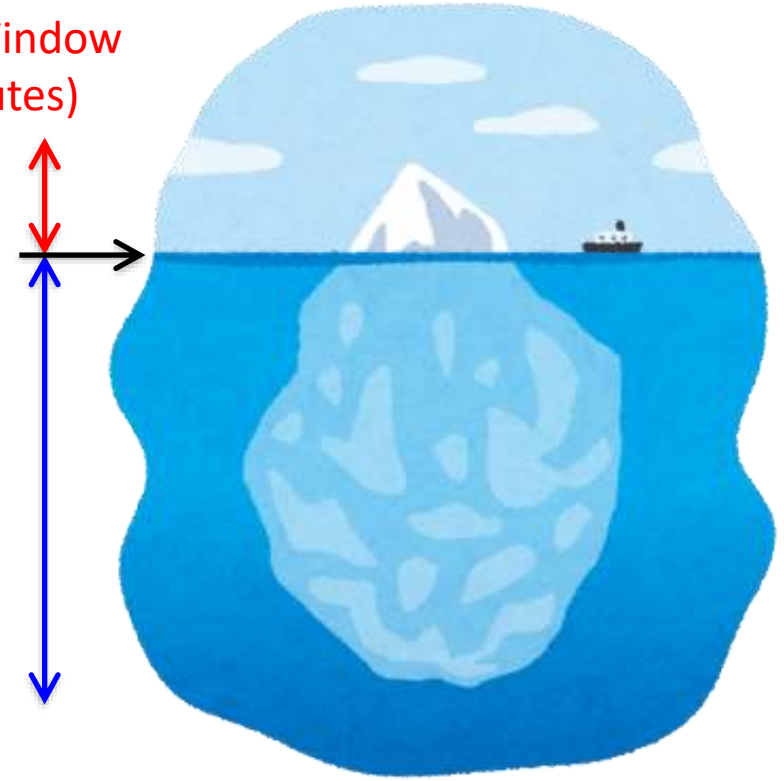
[Chair] Dr. Yoji SATO (NIHS)

Cell Therapy Products are Complex

Limited Characterization Window
(Observable Quality Attributes)

Limit of Knowledge

Unobservable
(but Potentially Critical)
Quality Attributes



Efficacy

Safety

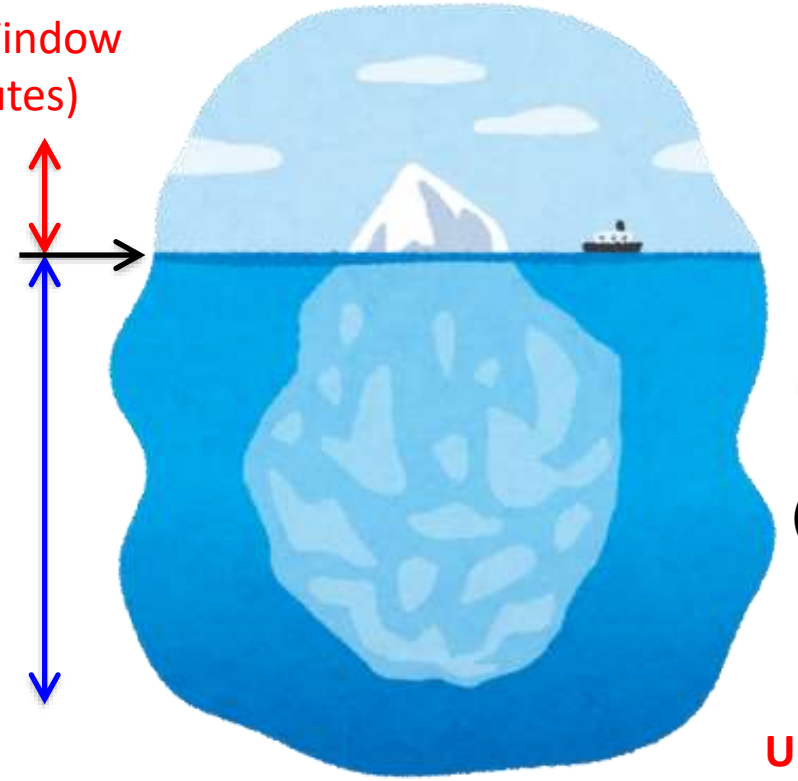
…which brings UNCERTAINTY in the comparability assessment

Cell Therapy Products are Complex

Limited Characterization Window
(Observable Quality Attributes)

Limit of Knowledge

Unobservable
(but Potentially Critical)
Quality Attributes



Efficacy

The mode of action (MOA) is unclear in many cases.

Understanding MOA would lead to **CQAs related to the efficacy** & ***in vitro* potency assays**.

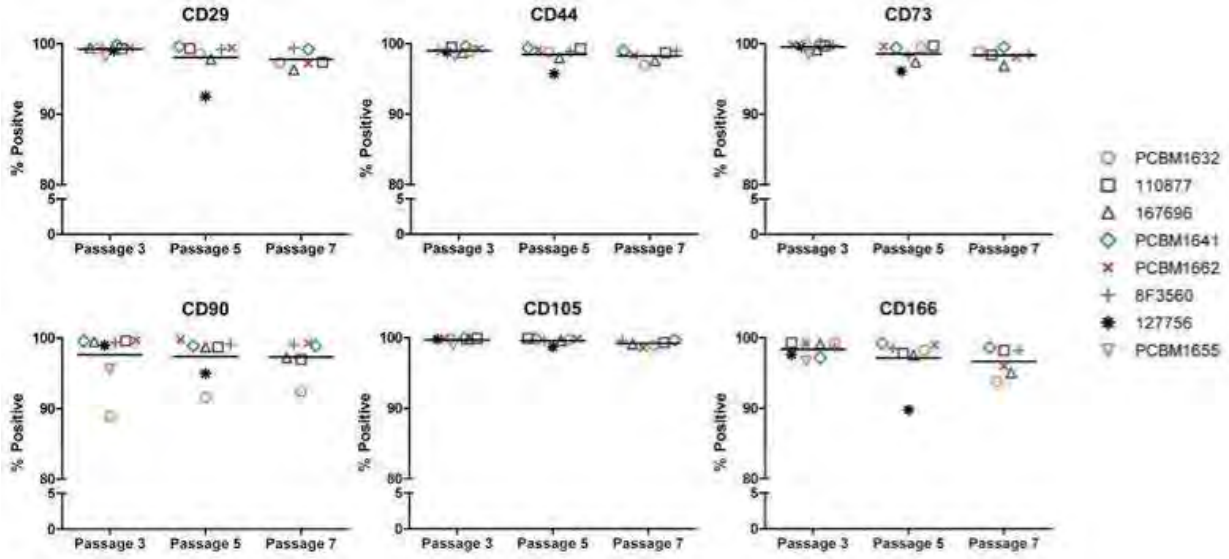
Useful Tools for Comparability Exercise

Provide Qualified Assays that Measure CQAs Predictive of Efficacy or Safety

EXAMPLE

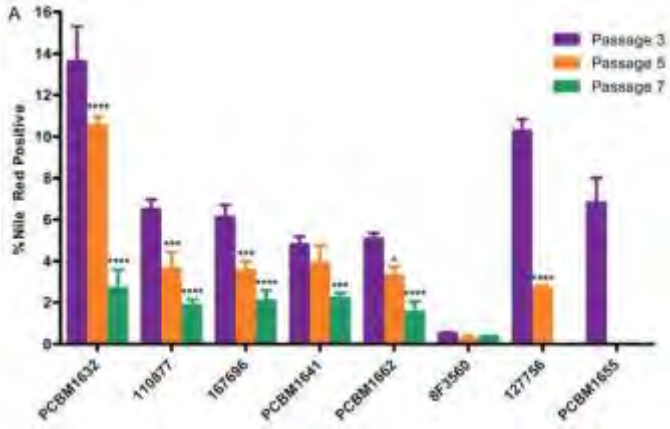
Lo Surdo JL *et al.,* Cytotherapy. 2013;15:1527-40.

MSCs **maintain expression of cell surface markers** through passages



But,

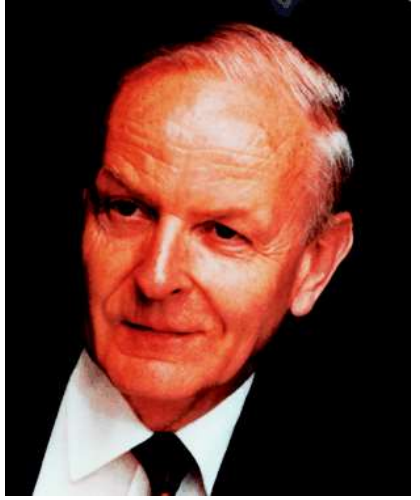
They show both **donor variability** and **decreased adipogenic potential** with increasing passage.



The "conventional" markers cannot be used for the comparability exercise, IF the product is expected to show this function.

Dr. Gerhard Zbinden

arguably the father of modern toxicology



- Do not do something just because you can.
- Do not do something just because it has always been done.
- Do not do something just because others do it.

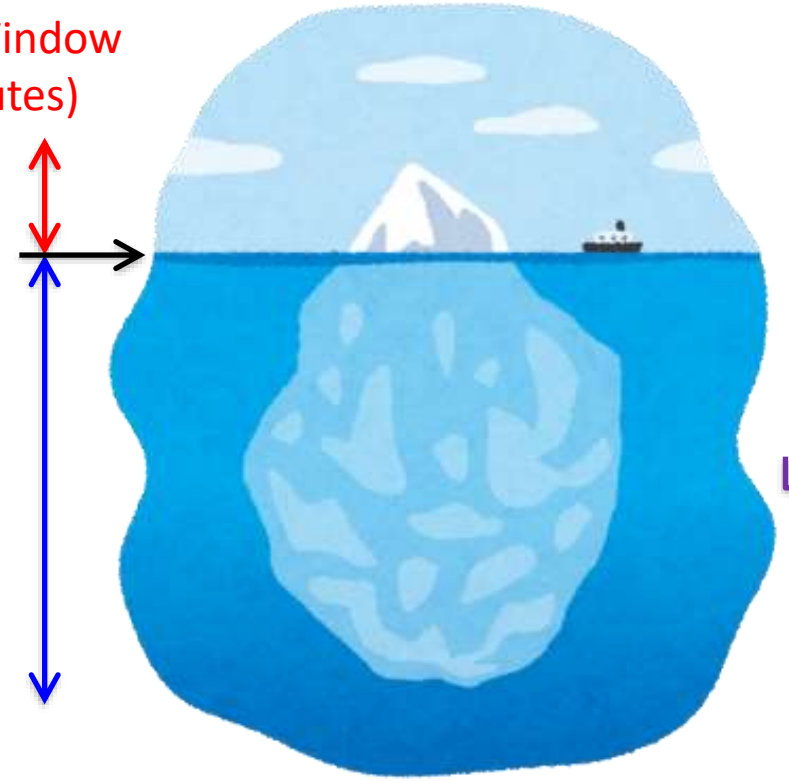
Hamlin RL, Toxicologic Pathology, 34:75–80, 2006

Cell Therapy Products are Complex

Limited Characterization Window
(Observable Quality Attributes)

Limit of Knowledge

Unobservable
(but Potentially Critical)
Quality Attributes



Safety

The risk mitigation should be comparable
(or more) after the change.

What can we do for the risk mitigation of CTPs at an early development phase?

Severity of Harm
Amount of Hazard
~~X Its Impact~~

X

~~Probability of Harm~~

=

Risk

In Case of Human-Derived CTPs

Non-clinical studies → Rejection and species difference in sensitivity

Little clinical experience → No Information about the probability of the harm

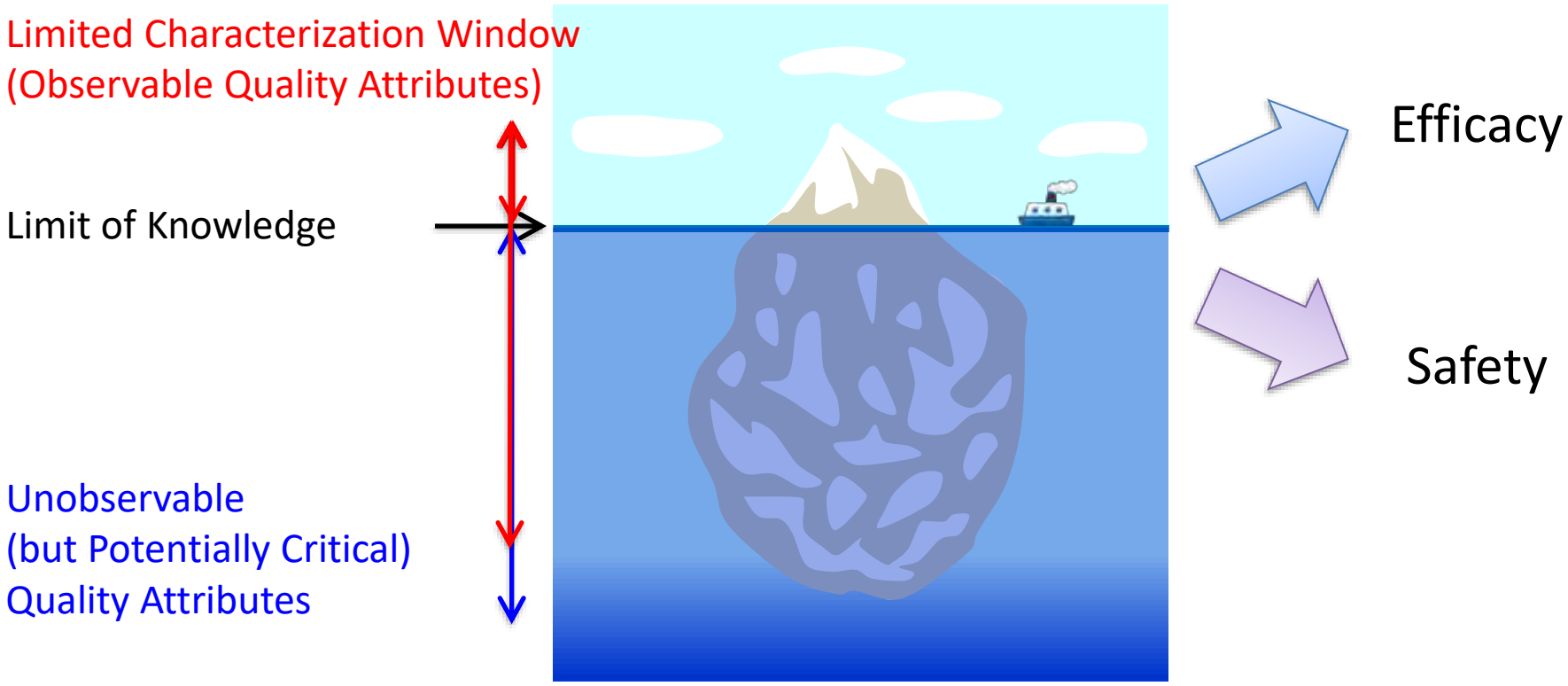
The basic strategy for the risk mitigation of human-derived CTPs is…

Identification, Quantitation and Reduction of Hazards

Comparability Assessment of the Quality of CTPs

- Discussions and development of guideline documents are underway in Japan regarding the comparability assessment of the quality of CTPs before and after the manufacturing process change.
- The concept of ICH Q5E can be applied to CTPs. However, CTPs are complex, and there is a limit to grasping quality attributes, so it is considered more difficult to evaluate the comparability, compared to conventional biopharmaceuticals.
- Understanding the mode(s) of action of a CTP and developing *in vitro* potency assays would be useful for assessing the quality associated with its efficacy.
- Understanding and controlling the heterogeneity of cells in products are big challenges in quality control and comparability assessment of CTPs.
- It is important to validate and qualify the test methods for the quality related to the product efficacy or safety.

Cell Therapy Products are Complex



For good comparability exercise of CTPs, it is necessary to develop more tools for "CQA Mining"

“Though the difficulties will be enormous when challenging these issues, our endeavors should not be lessened in order to better serve the public interest and health.”

Dr. Takao Hayakawa
Former Deputy Director General
National Institute of Health Sciences
(Chair, the MHLW drafting groups of the seven guideline documents on Q/S of CTPs and the MCP)

Thank you for your attention!

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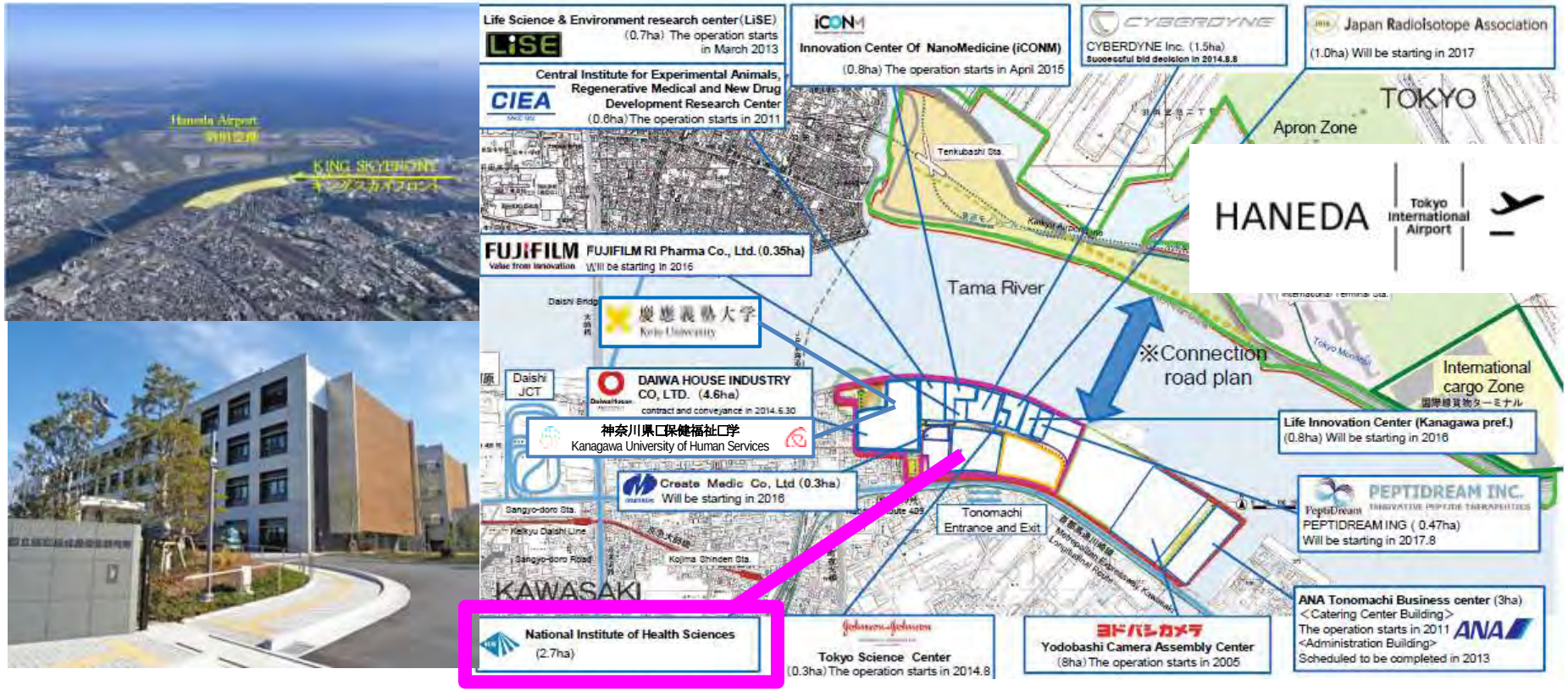

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* https://www.oag.com/hubfs/air-canada-787.jpg
** http://www.city.kawasaki.jp/en/page/0000038680.html