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Basic Approach for Comparability Assessment of Cell Therapy Products Subject to Changes in Their Manufacturing Process

Yoji SATO, Ph.D.

Head, Division of Drugs

(Immediate Former Head, Division of Cell-Based Therapeutic Products)

National Institute of Health Sciences, Japan

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Comparability

An essential requirement for quality when changing the manufacturing process of cell therapy products

Essential requirement for changes in the manufacturing process of biological products, including CTPs
細胞加工製品を含むバイオ医薬品等の製造工程の変更時の必須要件

- The changes in the manufacturing process should **not adversely affect the product safety and efficacy**.
  - It is reasonable and effective to judge the pros and cons of changing the manufacturing method by **evaluating changes in the quality characteristics of the product before and after the change**.
  - The need for confirmation in non-clinical and clinical trials is also determined by the content of the quality characteristics evaluation.

Comparable?

同等・同質?

- 製法変更によって少なくとも**製品の安全性と有効性に有害な影響を及ぼす変化がない**こと
  - 製法変更の是非は、変更前後の製品の**品質特性の変化を評価**することにより判断することが合理的かつ効果的。
  - 非臨床試験・臨床試験による確認尾必要性も、品質特性の評価の内容次第で判断。

“Comparable” 「同等・同質」 → ICH Q5E

- A conclusion that products **have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy**, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.

- **製造工程変更前後の製品が品質特性において高い類似性を有し、製剤の免疫原性を含む安全性、あるいは有効性に有害な影響が生じていないこと**をいう。これは、製品の品質特性の分析に基づき判断できることが多いが、非臨床試験や臨床試験のデータを勘案する必要がある場合もある。

Basic Approach for Assessment of Comparability Before and After Manufacturing Process Change (= ICH Q5E)
製法変更前後での同等性･同質性の評価の基本的考え方

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.

1. 製法変更前後の製品の品質特性の分析結果で評価･保証することを試みる。

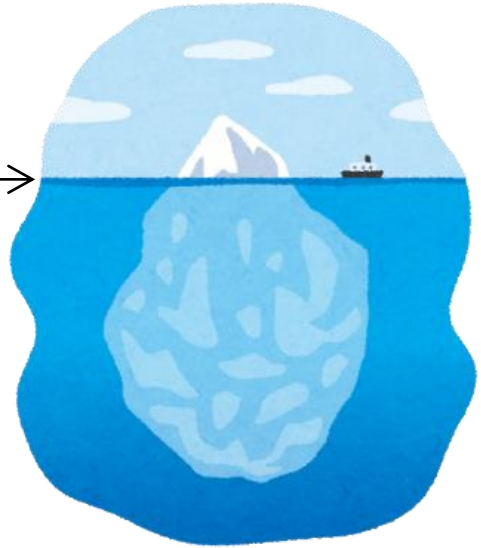
2. 製造工程変更前後の製品の品質特性に変化が認められ、また、品質特性と安全性及び有効性との関係が十分に解明されていないなどの理由により、同等性が十分に説明できない場合には、非臨床試験あるいは臨床試験の成績を組み合わせて評価する。

Cell Therapy Products are Complex
細胞加工製品は複雑

Limited Characterization Window
(Recognizable Quality Attributes)

Limit of Knowledge

Hidden/Unrecognizable
(but Potentially Critical)
Quality Attributes



Efficacy

Safety

…which creates UNCERTAINTY in the comparability assessment
(観察可能な)品質特性データのみで同等性を評価・保証することは難しいと予想される

Challenges in exploring and evaluating CQAs
CQAを探索・評価する際の課題

Test methods for viral safety, sterility, and tumorigenicity

- **Safety-related CQAs (characteristics and quantity of hazards)**

  Can you detect hazards and hazardous impurities that may have proliferative potential?

  Do you understand the sensitivity of your assays?

  = How can you avoid false negatives (and false positives)?

- **Efficacy-related CQAs**

  How do you identify attributes linked to cellular functions that

  … It's very difficult for products with unclear mechani

ウイルス安全性や無菌性
造腫瘍性の評価方法

- **安全性関連のCQA（ハザードの質と量）**

  増殖能を示すハザード・有害不純物を漏れなく検出できているか？測定法の感度を理解しているか？

  =偽陰性（＆偽陽性）の回避

- **有効性関連のCQA**

  有効性を裏付ける細胞機能とリンクした細胞特性をいかに同定する（掘り当てる）か？

  ・・・ 作用機序が明確でない製品の場合は、とても難しい

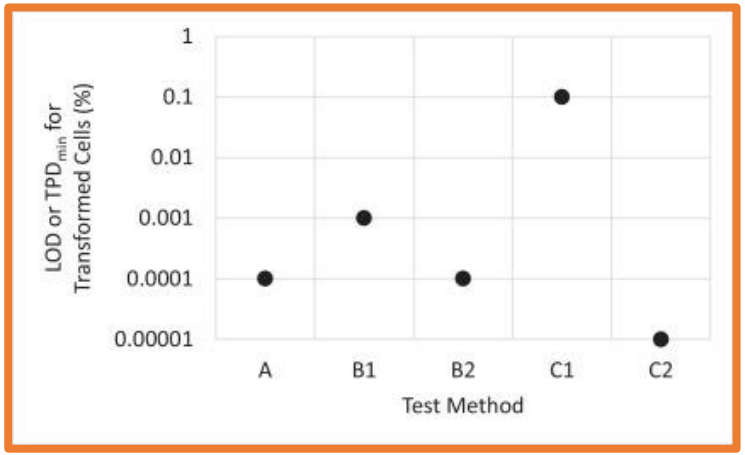
EXAMPLE

Sato Y, *et al., Cytotherapy.* 2019;21:1095-1111.

Limits of Detection (LODs) or Minimal Tumor Producing Doses (TPD_{min}) of Tumorigenic Cell Detection Tests

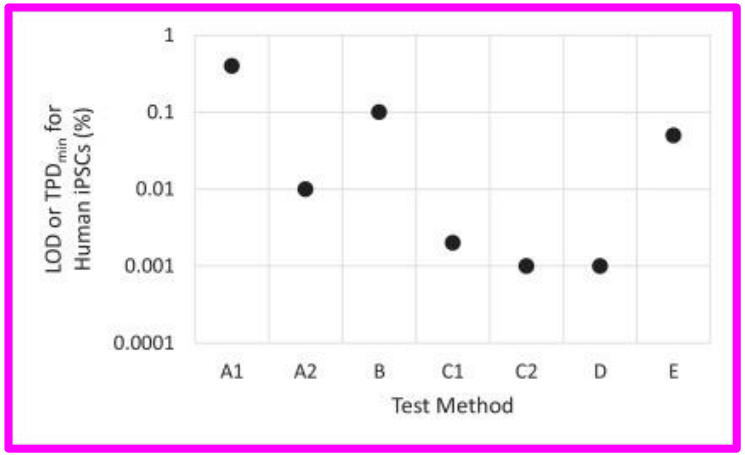
造腫瘍性細胞検出試験の検出限界(LODs)または最小腫瘍生成線量(TPDmin)

Transformed Cells in Normal Cells



A) TPD_{min} of ***in vivo*** **tumorigenicity test** (**HeLa cells/hMSC**, s.c. into NOG mice)
B1) LOD of **cell immortalization assay** (**immortalized hMSCs/hMSCs**)
B2) LOD of **cell immortalization assay** (**HeLa cells/hMSCs**)
C1) LOD of **conventional soft agar colony formation assay** (**HeLa cells/hMSCs**)
C2) LOD of **digital soft agar colony formation assay** (**HeLa cells/hMSCs**)

hiPSCs in Normal Cells



A1) TPD_{min} of ***in vivo*** **tumorigenicity test** (**hiPSCs/hRPE cells**, s.c. into NOG mice)
A2) TPD_{min} of ***in vivo*** **tumorigenicity test** (**hiPSCs/hNDF**, s.c. into NOG mice)
B) LOD of **flow cytometry** (**hiPSCs/hRPE cells**)
C1) LOD of **conventional qRT-PCR** (**hiPSCs/hRPE cells**)
C2) LOD of **droplet digital RT-PCR** (**hiPSCs/human cardiomyocytes**)
D) LOD of **highly efficient culture assay** (**hiPSCs/hMSCs**)
E) LOD of **GlycoStem-HP method** (**hiPSCs/HEK293 cells**).

Challenges in exploring and evaluating CQAs
CQAを探索・評価する際の課題

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  = How can you avoid false negatives (and false positives)?

- **Efficacy-related CQAs**

  How do you identify attributes linked to cellular functions that support efficacy?

  … It's very difficult for products with unclear mechanisms of action.

- **安全性関連のCQA（ハザードの質と量）**

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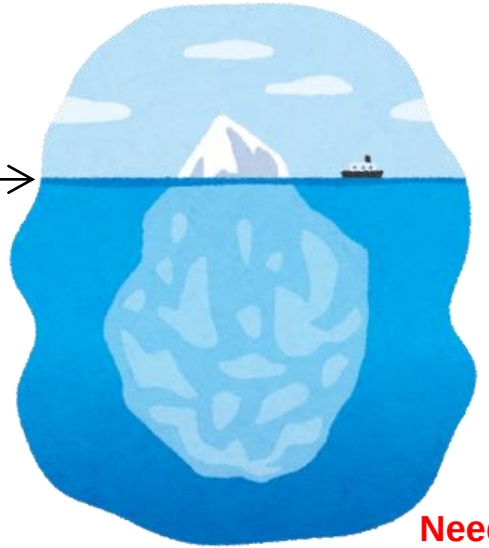


Efficacy

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

Need for understanding MOA and CQAs related to the efficacy or *in vitro* potency.

Need for a tool for uncovering hidden CQAs

Need for technology to understand heterogeneity
不均質性を理解するための技術が必要

For example, **even when there are a total of 1 million cells, only 10,000 of them may be effective**.

“Visualization” of such heterogeneity and **characterization of those 10,000 cells** would **make identifying CQAs related to efficacy easier.**

例えば、**総細胞数が100万個**あっても、**そのうち有効性を発揮するのは1万個**しかないという場合もありうる。

このような**不均質性を「見える化」**することで、**その1万個の細胞がどのような特性を持つのか**を明らかにすれば、 **有効性に関連するCQA（重要品質特性）を発見しやすくなる（・・・と期待できる）**

EXAMPLE

Stem Cells Translational Medicine, 2023, **12**, 379–390
https://doi.org/10.1093/stcltm/szad029
Advance access publication 2 June 2023
Original Research

NEW

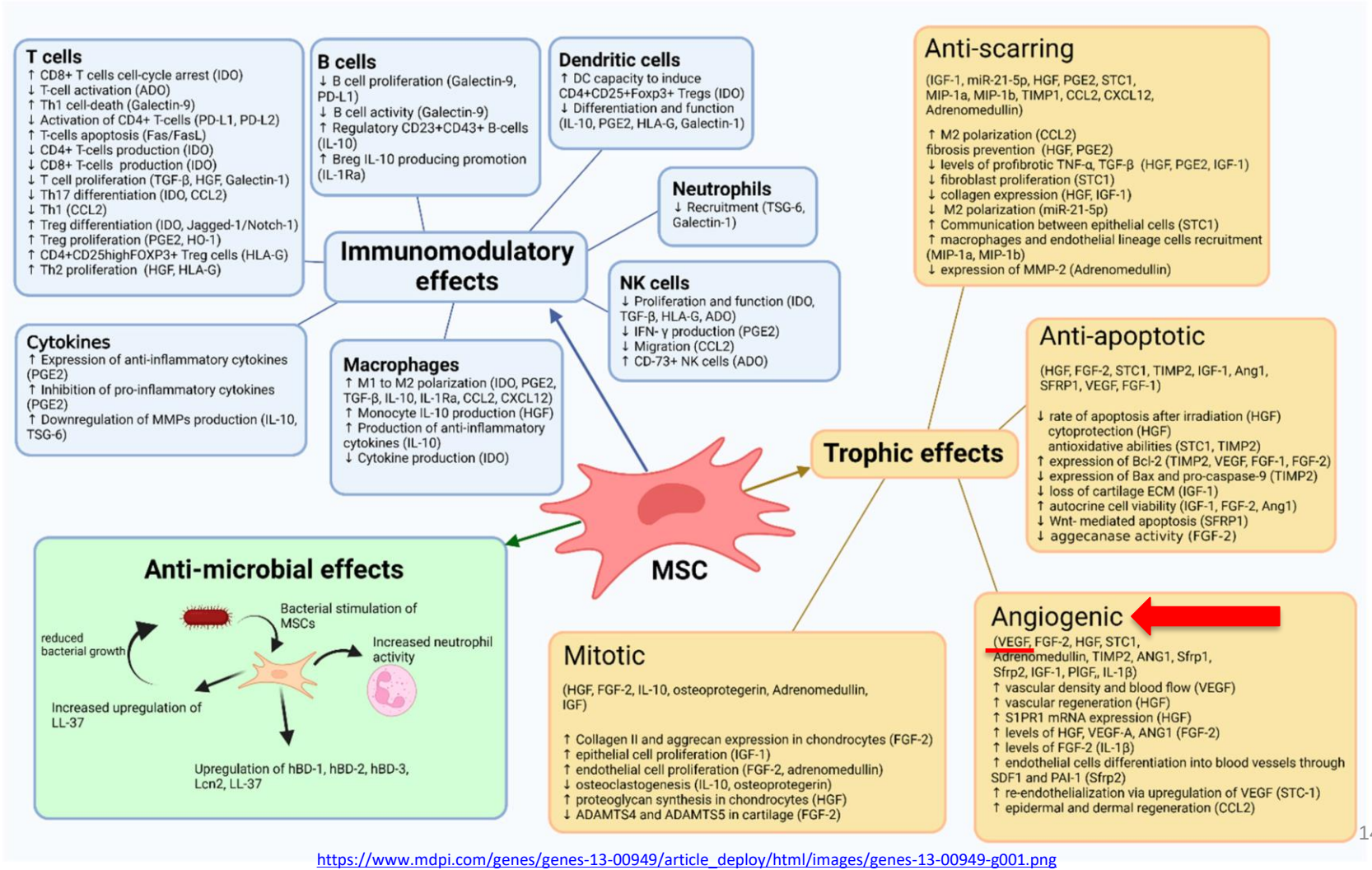
OXFORD

Single-Cell RNA-Seq Reveals *LRRC75A*-Expressing Cell Population Involved in VEGF Secretion of Multipotent Mesenchymal Stromal/Stem Cells Under Ischemia

Takumi Miura[1,2,‡], Tsukasa Kouno[3,‡], Megumi Takano[1], Takuya Kuroda[1], Yumiko Yamamoto[3], Shinji Kusakawa[1], Masaki Suimye Morioka[3], Tohru Sugawara[2,4], Takamasa Hirai[1], Satoshi Yasuda[1], Rumi Sawada[1], Satoko Matsuyama[1,5], Hideya Kawaji[3,6], Takeya Kasukawa[3], Masayoshi Itoh[3], Akifumi Matsuyama[5], Jay W. Shin[3,7], Akihiro Umezawa[2], Jun Kawai[3,8], Yoji Sato[*,1,8,9]

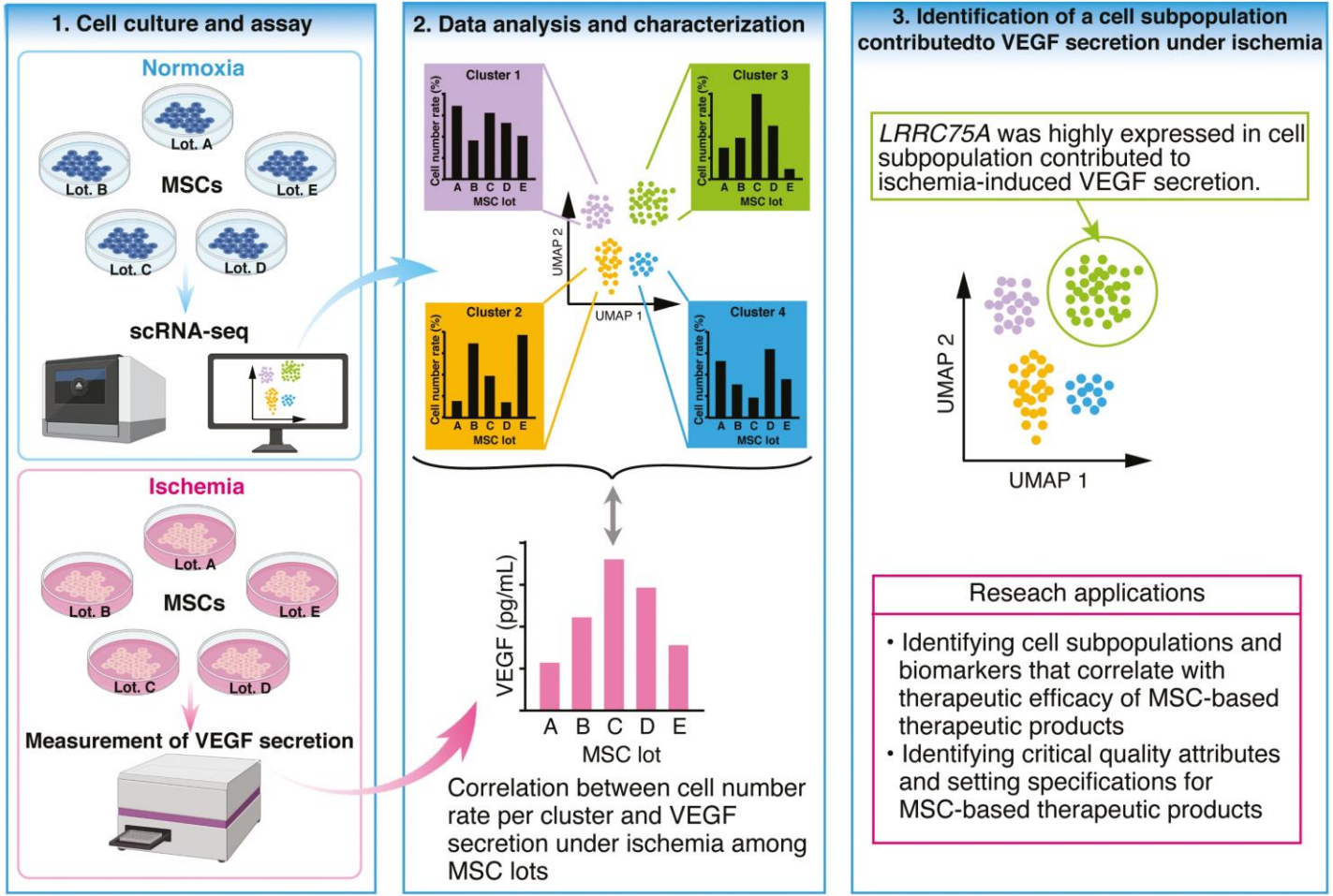
[1]Division of Cell-Based Therapeutic Products, National Institute of Health Sciences, Kanagawa, Japan
[2]Center for Regenerative Medicine, National Center for Child Health and Development, Tokyo, Japan
[3]RIKEN Center for Integrative Medical Sciences, Yokohama, Japan
[4]Biopharmaceutical and Regenerative Sciences, Graduate School of Medical Life Science, Yokohama City University, Yokohama, Japan
[5]Center for Reverse TR, Osaka Habikino Medical Center, Osaka Prefectural Hospital Organization, Osaka, Japan
[6]Research Center for Genome & Medical Sciences, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
[7]Genomic Institute of Singapore, Agency for Science, Technology and Research, Singapore
[8]Life Science Technology Project, Kanagawa Institute of Industrial Science and Technology, Kawasaki, Japan
[9]Department of Cellular and Gene Therapy Products, Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan

[*]Corresponding author: Yoji Sato, PhD, Division of Cell-Based Therapeutic Products, National Institute of Health Sciences, 3-25-26 Tonomachi, Kawasaki Ward, Kawasaki City, Kanagawa 210-9501, Japan. Email: yoji@nihs.go.jp
‡Contributed equally.



https://www.mdpi.com/genes/genes-13-00949/article_deploy/html/images/genes-13-00949-g001.png

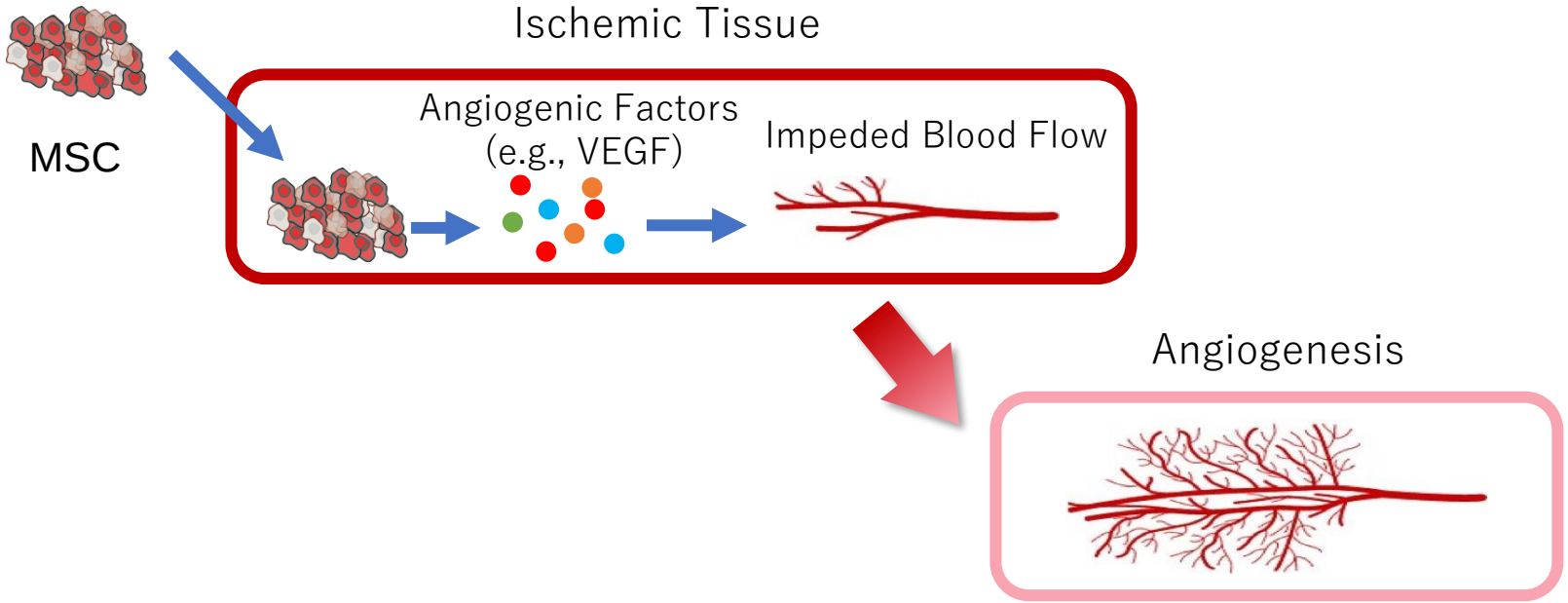
Evaluation of MSC heterogeneity by single-cell RNA-Seq



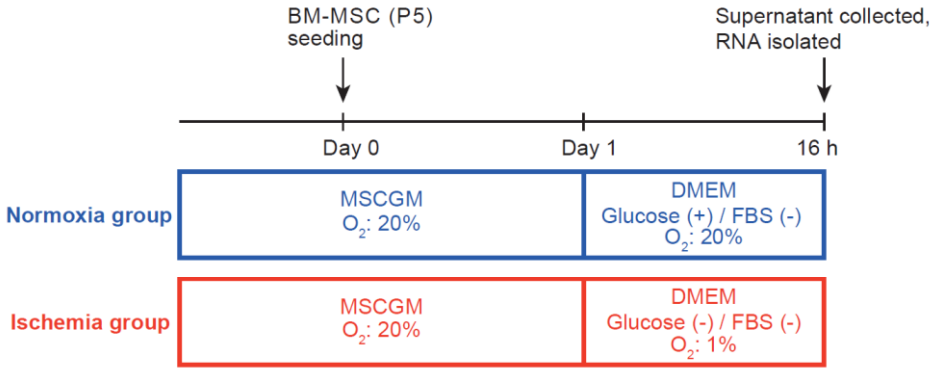
Miura T *et al.*, *Stem Cells Transl Med.* 2023;**12**:379-390.

https://doi.org/10.1093/stcltm/szad029

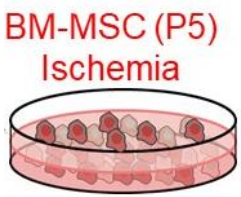
Design of an experimental condition mimicking the environment of the engraftment site

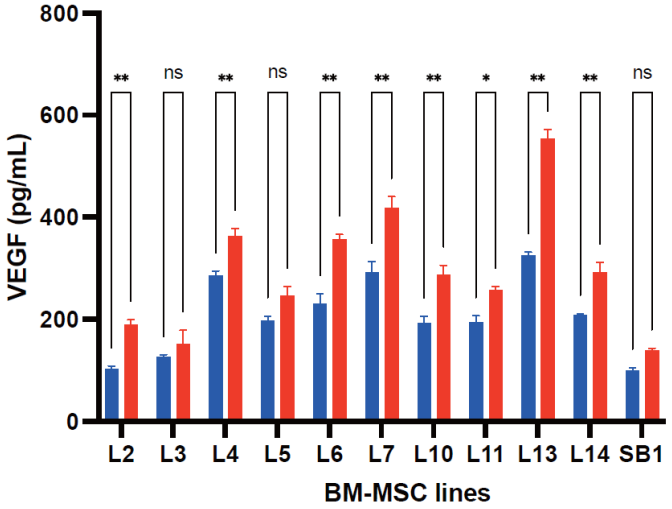


Design of an experimental condition mimicking the environment of the engraftment site



BM-MSCs under ischemia





an indicator of potency

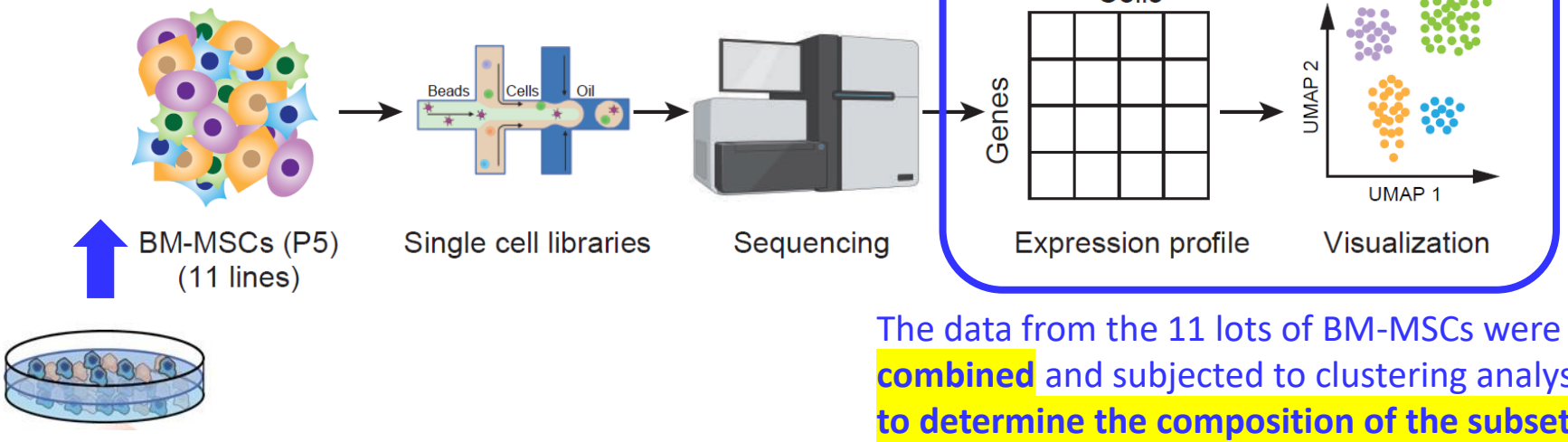
VEGF secretion varies widely between the lines.

Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

Single-Cell Transcriptome Experiments

BM-MSCs under normoxia

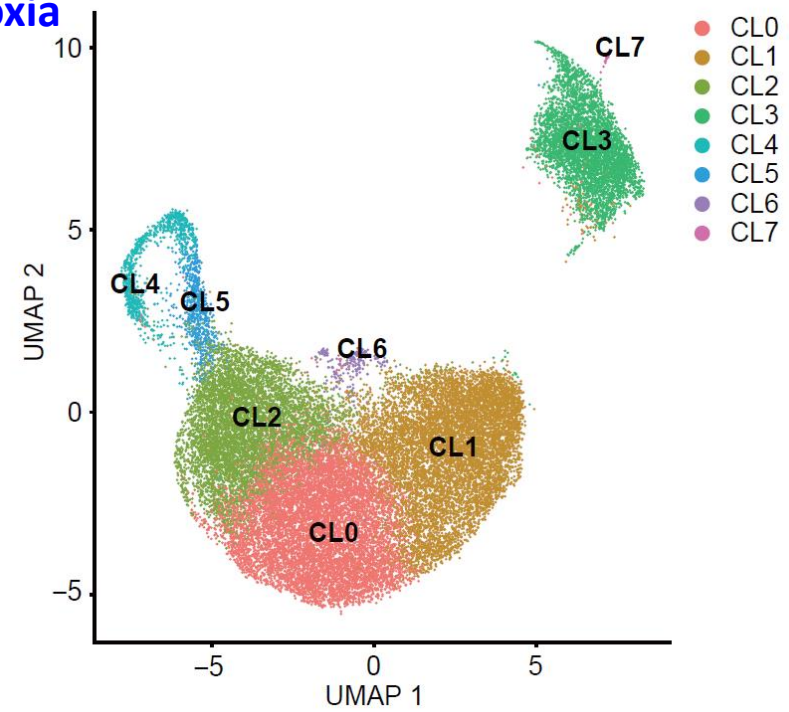


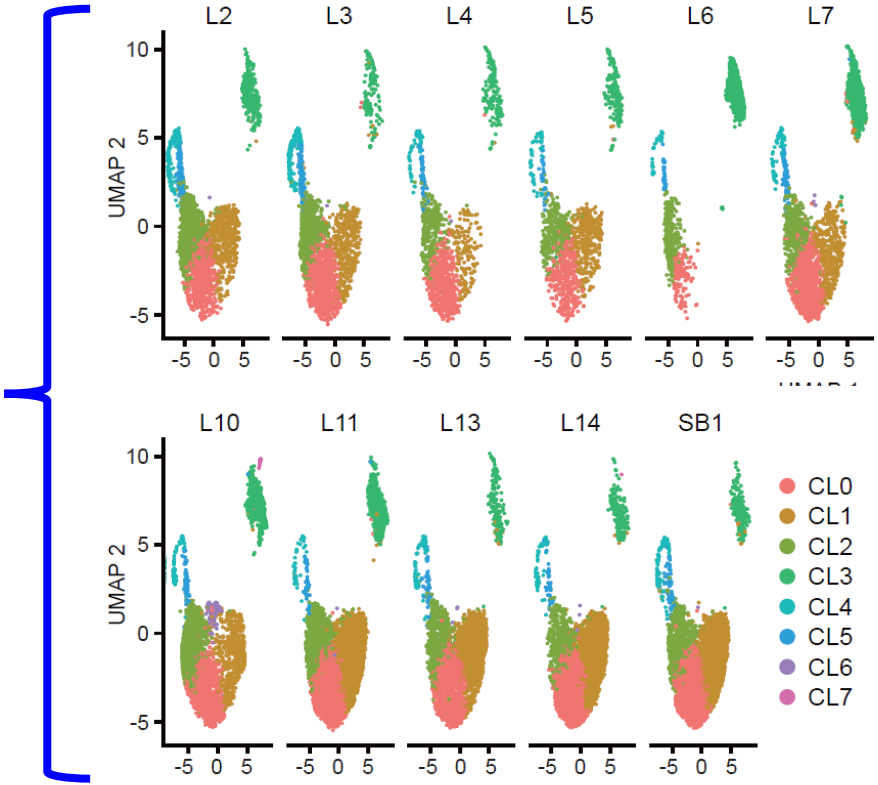
The data from the 11 lots of BM-MSCs were **combined** and subjected to clustering analysis **to determine the composition of the subsets of "average BM-MSCs" (BM-MSCs as a population)**.

Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

Single-Cell Transcriptome Experiments

BM-MSCs (P5)
Normoxia





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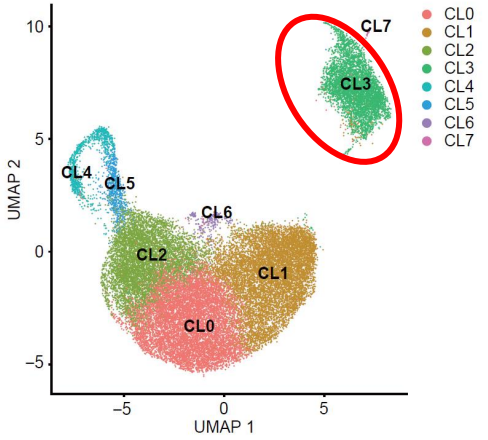
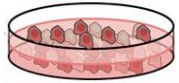
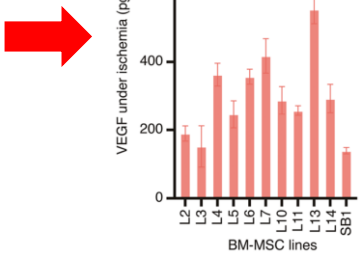
Single-Cell Transcriptome Experiments

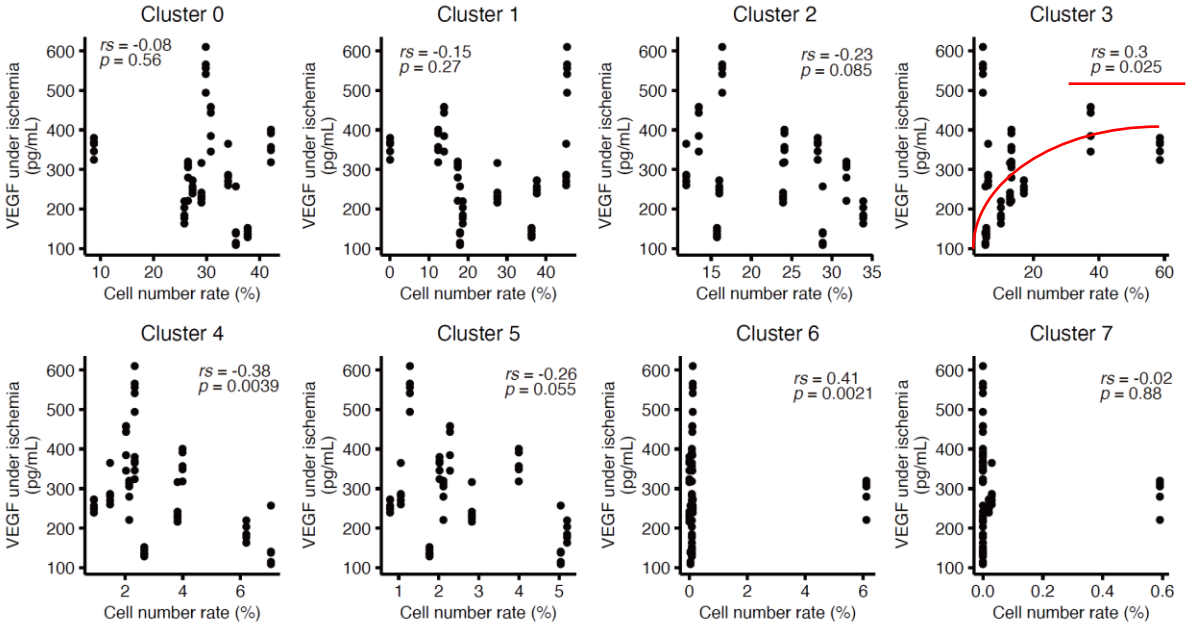
BM-MSCs (P5)
Normoxia



BM-MSC (P5)
Ischemia



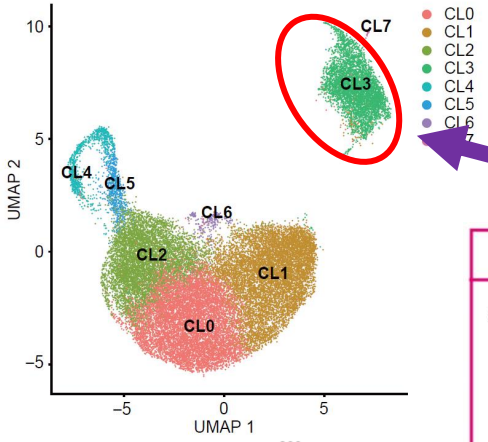




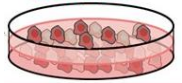
Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

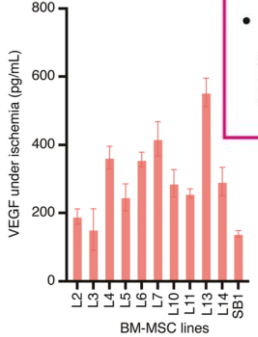
Functional involvement of LRRC75A

BM-MSCs (P5)
Normoxia



BM-MSC (P5)
Ischemia

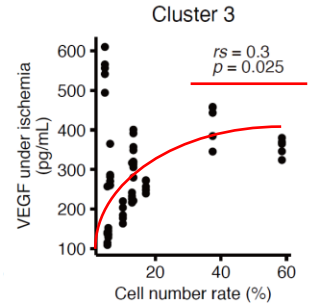




Top 20 upregulared genes of CL3

Gene name	Ave $\log_2$FC
LRRC75A	1.0357
KRT7	0.8382
KRT16	0.7902
[illegible]	0.7815
FLG	0.6049
SH3BGRL3	0.5970
TPM2	0.5859
POLR2L	0.5555
GADD45B	0.5543

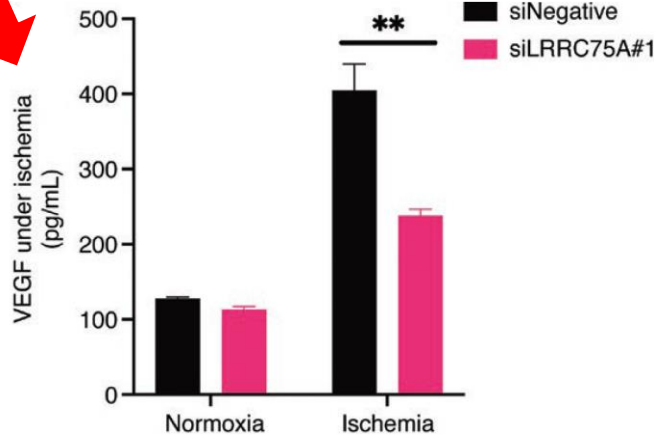
Hidden CQAs



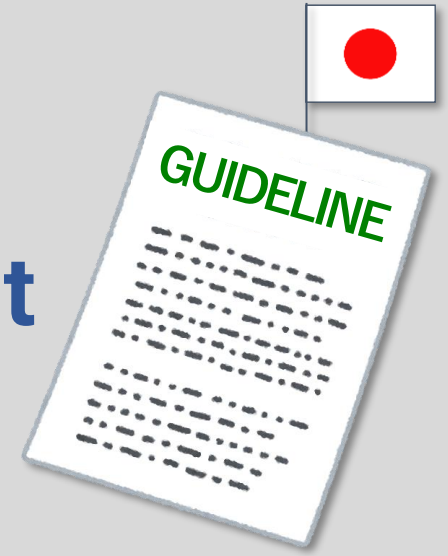
Reseach applications

- Identifying cell subpopulations and biomarkers that correlate with therapeutic efficacy of MSC-based therapeutic products
- Identifying critical quality attributes and setting specifications for MSC-based therapeutic products

***LRRC75A* is functionally involved in VEGF secretion during ischemia.**



A Draft Guideline Document



AMED Research Project (FY2019-FY2021)

“Research on the Comparability Assessment of Cell-Processed Products Subject to Changes in Their Manufacturing Process”

[The Japanese draft is already available at: https://www.amed.go.jp/content/000108765.pdf]

AMED Research Project (FY2019-FY2021)
“Research on the Comparability Assessment of Cell-Processed Products Subject to Changes in Their Manufacturing Process”

AMED研究事業（2019年度−2021年度）
「細胞加工製品の製造工程の変更に伴う同等性／同質性評価のあり方に関する研究」

➢メンバー

荒戸　照世（北海道大学）

内田　和久（神戸大学）

梅澤　明弘（国立成育医療研究センター）

岡崎　利彦（大阪大学）

紀ノ岡正博（大阪大学）

笹井　雅夫（大阪大学）

佐藤　陽治（国立医薬品食品衛生研究所；座長）

早川　堯夫（国立医薬品食品衛生研究所,
前 ICH Q5E 専門家作業部会ラポーター）

➢Members

Teruyo ARATO (Hokkaido Univ.)

Kazuhisa UCHIDA (Kobe Univ.)

Akihiro UMEZAWA (NCCHD)

Toshihiko OKAZAKI (OSAKA Univ.)

Masahiro KINO-OKA (Osaka Univ.)

Masao SASAI (OSAKA Univ.)

Yoji SATO (NIHS, Chair)

Takao HAYAKAWA (NIHS,
the Former Rapporteur of ICH Q5E EWG)

GUIDELINE FOR COMPARABILITY OF HUMAN CELL-PROCESSED PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (DRAFT)

ヒト細胞加工製品の製造工程の変更に伴う同等性／同質性評価に関する指針（案）

1.2 背景

・・・ 既存のICHガイドラインや国内関連法令等には、ヒト細胞加工製品の製造工程変更前後の製品の同等性／同質性を実証するために考慮すべき事項に焦点をあてた記載はなされていない。しかしいくつかのICHガイドラインや国内関連法令等においては、参考となる技術的情報が示されており、これらはヒト細胞加工製品の製造工程変更に伴う評価に際しても有用と考えられる（本文書「参考文献」の項に代表例を示す）。本文書は、主にICH Q5Eガイドライン「生物薬品（バイオテクノロジー応用医薬品／生物起源由来医薬品）の製造工程の変更にともなう同等性／同質性評価」の内容を踏まえつつ、ヒト細胞加工製品の製造工程変更前後の製品の同等性／同質性を実証するために品質特性評価の面からアプローチを行う際に必要な指針を提供するものである。

1.2 Background

… The existing ICH documents and relevant domestic laws and regulations have not specifically addressed considerations for demonstrating comparability of human cell-processed products before and after a change to the manufacturing process. However, several ICH documents and relevant domestic laws and regulations have provided referential technical information that can also be useful for assessing process changes for human cell-processed product. (Representative examples are shown in the “References” section of this document.) This document is intended to provide the guidelines necessary to take an approach in terms of quality characterization to demonstrate the comparability of human cell-processed products before and after a change to the manufacturing process, mainly based on the ICH Q5E guideline “Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.”

ICH Q5E: COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

ICH Q5E：生物薬品（バイオテクノロジー応用医薬品／生物起源由 来医薬品）の製造工程の変更にともなう同等性／同質性評価

1.0 緒言
- 1.1 本ガイドラインの目的
- 1.2 背景
- 1.3 適用対象
- 1.4 一般原則

2.0 ガイドライン
- 2.1 同等性／同質性評価作業に関する留意事項
- 2.2 品質に関する留意事項
  - *2.2.1 分析法*
  - *2.2.2 特性解析*

1.0 INTRODUCTION
- 1.1 Objectives of the Guideline
- 1.2 Background
- 1.3 Scope
- 1.4 General Principles

2.0 GUIDELINES
- 2.1 Considerations for the Comparability Exercise
- 2.2 Quality Considerations
  - *2.2.1 Analytical Techniques*
  - *2.2.2 Characterisation*

GUIDELINE FOR COMPARABILITY OF HUMAN CELL-PROCESSED PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (DRAFT)

ヒト細胞加工製品の製造工程の変更に伴う同等性／同質性評価に関する指針（案）

ICH Q5E: COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

ICH Q5E：生物薬品（バイオテクノロジー応用医薬品／生物起源由 来医薬品）の製造工程の変更にともなう同等性／同質性評価

2.2.3 規格及び試験方法

2.2.4 安定性

2.3 製造工程に関する留意事項

2.4 開発段階における製造工程変更時の同等性／同質性

2.5 非臨床試験及び臨床試験に関する留意事項

2.5.1 非臨床試験及び臨床試験を計画する際考慮すべき要素

2.5.2 試験の種類

3.0 用語集

4.0 参考文献

2.2.3 Specifications

2.2.4 Stability

2.3 Manufacturing Process Considerations

2.4 Demonstration of Comparability during Development

2.5 Nonclinical and Clinical Considerations

2.5.1 Factors to be Considered in Planning Nonclinical and Clinical Studies

2.5.2 Type of Studies

3.0 GLOSSARY

4.0 REFERENCES

GUIDELINE FOR COMPARABILITY OF HUMAN CELL-PROCESSED PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (DRAFT)

ヒト細胞加工製品の製造工程の変更に伴う同等性／同質性評価に関する指針（案）

GUIDELINE FOR COMPARABILITY OF HUMAN CELL-PROCESSED PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (DRAFT)

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GUIDELINE FOR COMPARABILITY OF HUMAN CELL-PROCESSED PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (DRAFT)

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1.3.2 適用対象製品の特徴（抜粋）

「適用対象となるヒト細胞加工製品は、『医薬品，医療機器等の品質，有効性及び安全性の確保等に関する法律』に定められる再生医療等製品のうち、人の細胞に培養その他の加工を施すことにより製造されるものを指す。ヒト細胞加工製品は複雑で不均一な生細胞を成分として含むため、CQAを網羅的に観察することができるとは限らないこと、及び遺伝子組換え体細胞又は非組換え体細胞のタンパク質発現系から培養により産生されて高度に精製されることにより製造される生物薬品（バイオテクノロジー応用医薬品／生物起源由来医薬品）のように既存の一連の分析方法を用いての特性解析が可能であるとは限らないことに留意する必要がある。一方、ヒト細胞加工製品の同等性／同質性評価においては、特性解析のみならず、他の要因（例えば変更する製造工程の原理的な差分の説明を含めた評価を加えて判断することもありうる。個別製品の製造工程の変更に伴う同等性／同質性評価の充足性については、製造販売業者は規制当局に相談すること。・・・」

1.3.2 Characteristics of Applicable Products (excerpts)

“Applicable human cell-processed products shall refer to regenerative medicine products specified in the “Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices” that are manufactured by culturing or otherwise processing human cells. Because human cell-processed products contain complex and heterogeneous viable cell components, it should be noted that **their CQAs cannot always be observed comprehensively**, and that **they cannot always be characterized using an existing set of analytical procedures like biopharmaceuticals (biotechnological/biological products)**, which are produced from recombinant or non-recombinant somatic cell protein expression systems by culture and highly purified. **On the other hand, it is also possible that, in the evaluation of the comparability of human cell-processed products, the decision may be made not only on the basis of characterization, but also on other factors (e.g., rationale differences in the manufacturing process to be changed).** As for the sufficiency of the comparability assessment following changes in the manufacturing process of individual products, the manufacturer should consult with the relevant regulatory authority. …”

GUIDELINE FOR COMPARABILITY OF HUMAN CELL-PROCESSED PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS (DRAFT)

ヒト細胞加工製品の製造工程の変更に伴う同等性／同質性評価に関する指針（案）

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1. 4. 2 ヒト細胞加工製品の同等性／同質性評価作業における基本的考え方（抜粋）

「低分子医薬品やICH Q5Eが対象とするバイオテクノロジー応用医薬品とは異なり、ヒト細胞加工製品の場合、有効成分である細胞の品質特性を分子レベルで網羅的に解析及び提示することが著しく困難であり、その一方で細胞集団の不均一性、並びに周辺環境の影響による細胞の形質の変化（例えば分化や脱分化）及び周辺環境に対する細胞の応答（例えば生理活性物質の放出）などを検討することが重要である。

従って、ヒト細胞加工製品では、現時点の技術で測定可能な品質特性をすべて挙げたとしても、有効性及び安全性の同等性／同質性を十分に保証するために必要な必須品質特性すべてを完全に網羅・同定できているとは限らない。 ・・・」

1.4.2 Basic Concepts for Comparability Exercise of Human Cell-Processed Products (excerpts)

“Unlike low-molecular-weight pharmaceuticals and biotechnological products subject to ICH Q5E, **for human cell-processed products, there are significant difficulties in comprehensively analyzing and presenting the quality attributes of cells as the active ingredient at a molecular level**, whereas **it is important to examine the heterogeneity of cell population, phenotypical changes attributable to the surrounding environment (e.g., differentiation and dedifferentiation), and cellular responses to the surrounding environment (e.g., release of bioactive substances)**.

Therefore, **even if all quality attributes measurable with current technology are listed for human cell-processed products, it may not always be assured that all critical quality attributes necessary to fully assure the comparability of efficacy and safety have been completely covered and identified.** …”

Conclusions

- Because of the complexity and heterogeneity of the cells as the active ingredient of cell therapy products (CTPs), even if we list all of the quality attributes that we can recognize, it may not be possible to fully identify and encompass all of the CQAs necessary to assure the efficacy and safety of the CTPs after their manufacturing changes.
- **Avoidance of false negatives is critical in the evaluation of safety-related CQAs, and it is important to understand the sensitivity and specificity of the test methods.**
- **Identification of cell subpopulations and biomarkers that correlate with potency/efficacy through single-cell transcriptome analysis and other methods, and use of these as CQAs, will help establish manufacturing methods to reproducibly produce effective CTPs.**
- **In Japan, the draft guideline document for the comparability assessment of CTPs subject to changes in their manufacturing process has been prepared, based on ICH Q5E.**

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- 細胞治療製品（CTP）の有効成分である細胞は複雑で不均質であるため、認知しうる品質特性をすべて列挙したとしても、製造変更後のCTPの有効性と安全性を保証するために必要なCQAをすべて特定・網羅することはできない可能性がある。
- **安全性関連のCQAの評価においては偽陰性の回避が最重要課題であり、試験法の感度や特異度を把握することが重要である。**
- **シングル・セル・トランスクリプトーム解析などにより、力価／有効性と相関する細胞亜集団やバイオマーカーを同定し、これらをCQAとすることは、有効な細胞治療製品を再現性高く製造する製法の確立に役立つと考えられる。**
- **CTPの製法変更前後の品質の同等性評価に関するガイドラインは、日本でもICH Q5Eをもとに準備中である。**

Thank You

Yoji SATO, Ph.D.
Head, Division of Drugs, National Institute of Health Sciences, Kanagawa, Japan
E-mail: yoji@nihs.go.jp