The 24th JSRM Congress
March 22, 2025, Yokohama

シンポジウム27　再生･細胞治療の産学連携拠点で解決すべき問題とはなにか

Scientific Understanding of the Value of Cell Therapy Products
再生医療／細胞加工製品の価値の科学的理解

Yoji SATO, Ph.D.

Head, Division of Drugs, National Institute of Health Sciences

Visiting Professor, School of Health Innovation, Kanagawa University of Human Services

Adjunct Research Scientist, Kanagawa Institute of Industrial Science and Technology

DISCLAMER

再生医療／細胞加工製品の価値の科学的理解

佐藤陽治
国立医薬品食品衛生研究所
薬品部

筆頭演者は、過去１年間（1月～12z月）において、本演題の発表に関して開示すべきCOIはありません。

本発表で述べられた見解・意見は発表者のものであり、必ずしも国立医薬品食品衛生研究所または厚生労働省の公式な方針や見解を示すものではありません。

Scientific Understanding of the Value of Cell Therapy Products

Yoji Sato, Ph.D.,
Division of Drugs,
National Institute of Health Sciences

For the past year (January-December), the speaker has no COI to disclose for this presentation

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

What is “the value of medicine” expressed by?

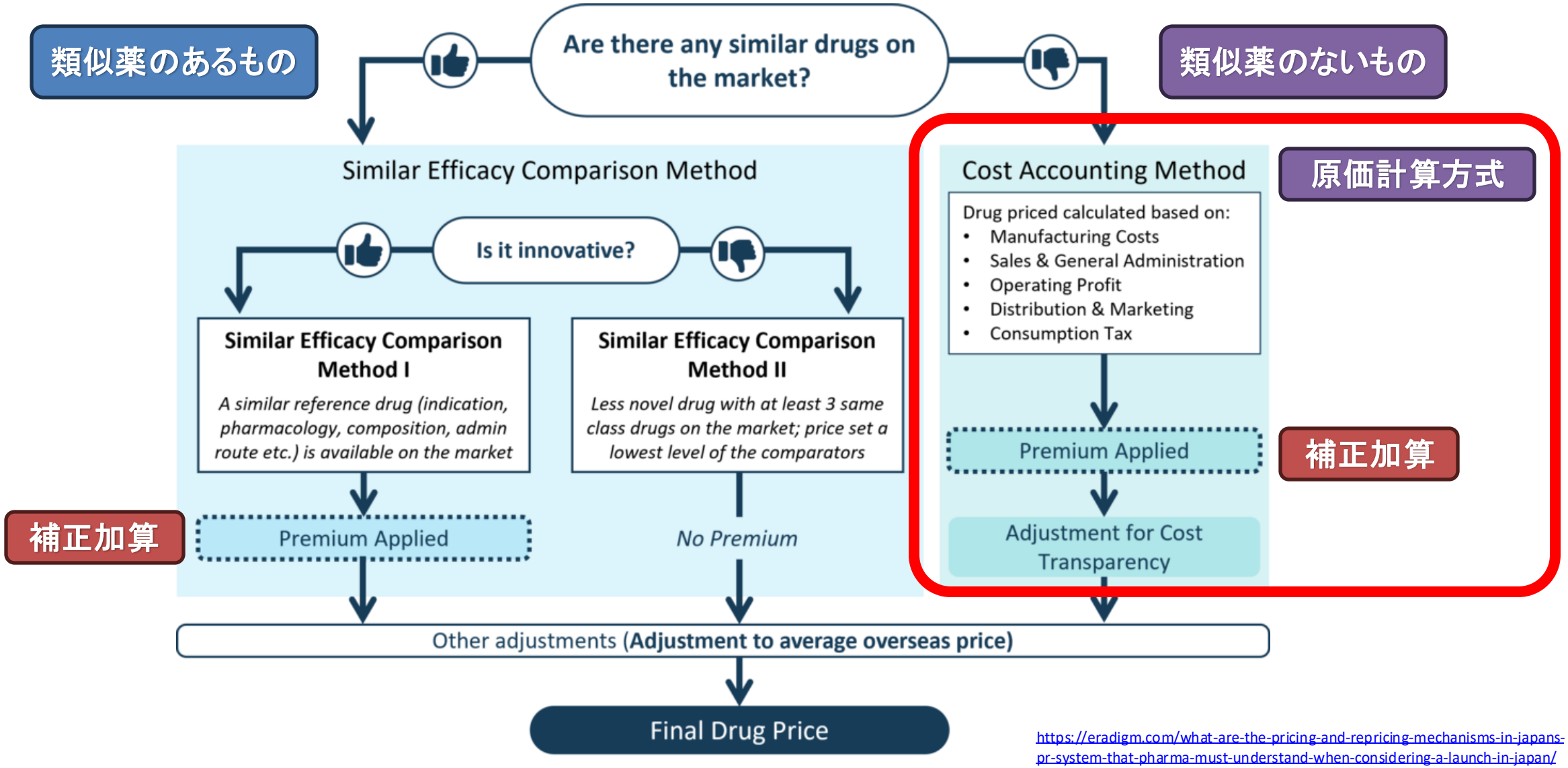
「医薬の価値」とは何によって表現されるか？

Drug Price

薬価

Japan's Pricing System for New Pharmaceuticals

日本における新医薬品の薬価算定方式



https://eradigm.com/what-are-the-pricing-and-repricing-mechanisms-in-japans-pr-system-that-pharma-must-understand-when-considering-a-launch-in-japan/

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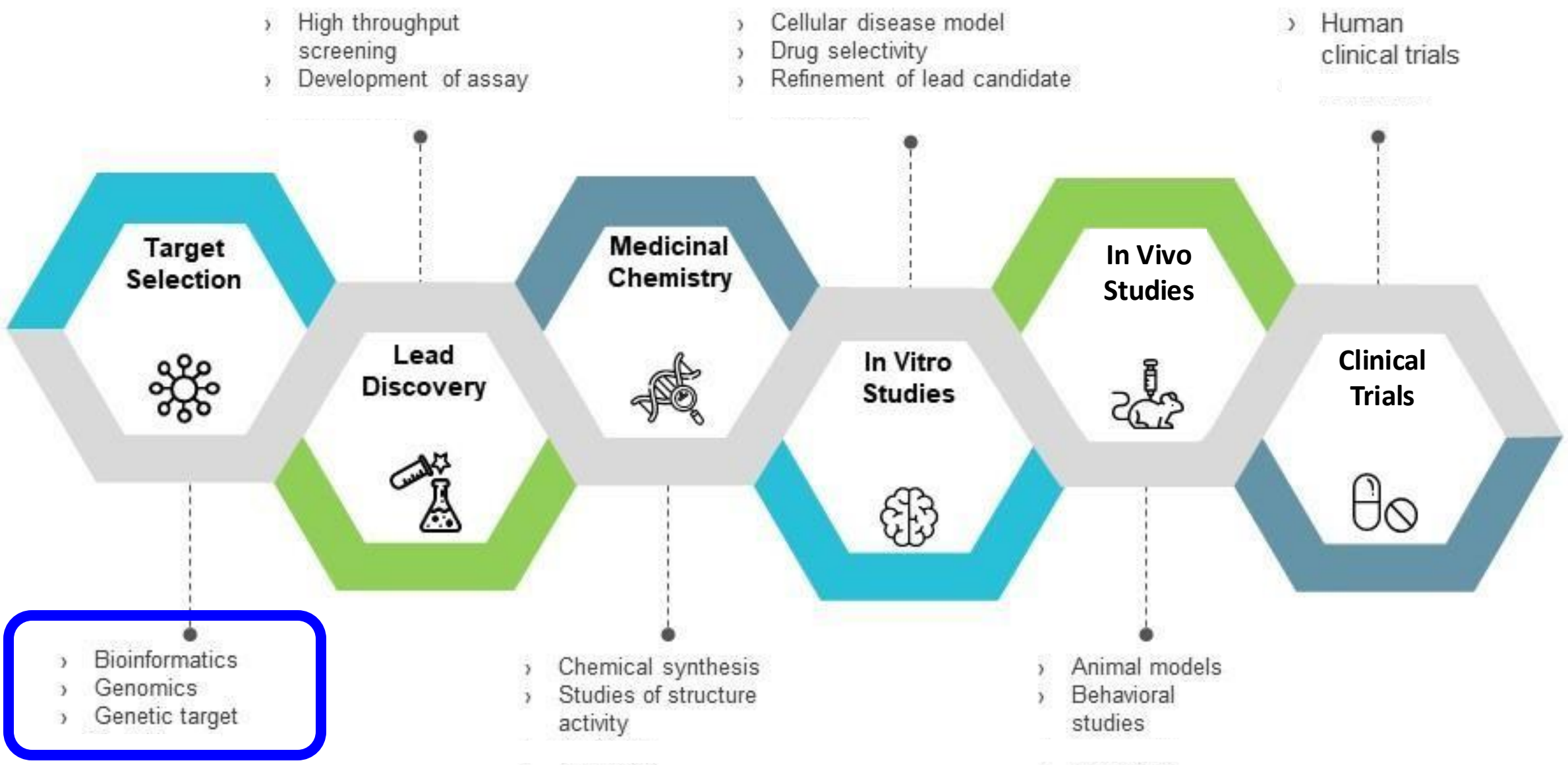
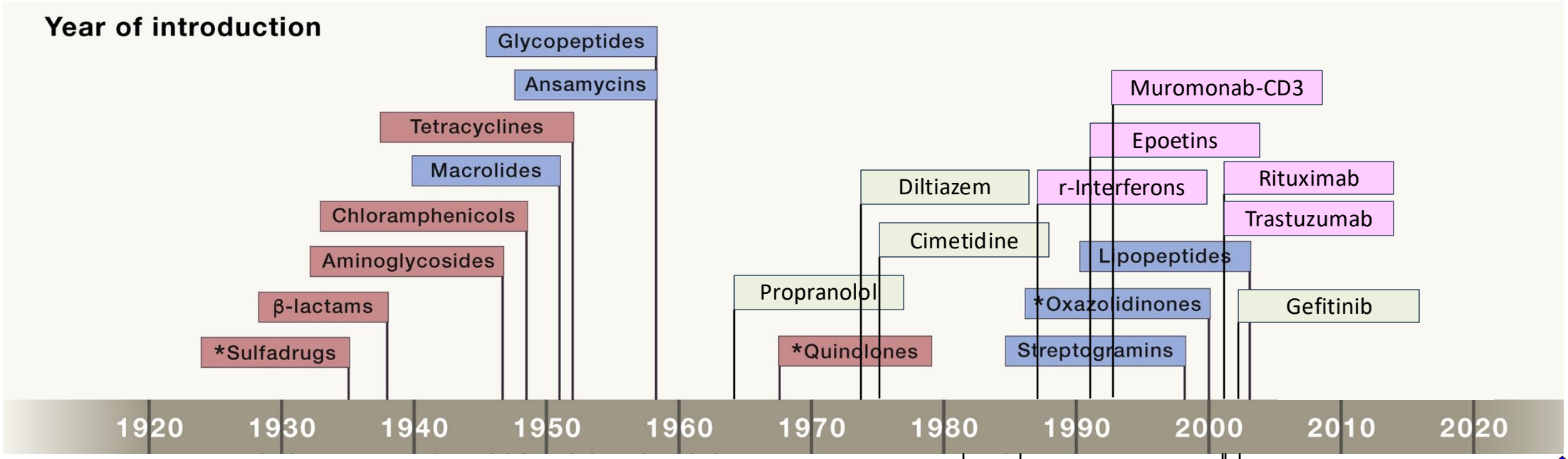
Recent Drug Development 最近の新医薬品開発



Pharmatalks community 21 Dec 2023 https://www.linkedin.com/pulse/unveiling-new-drug-development-process-analytical-method-validation-kdmef/

The Timeline of Drug Discovery 主な創薬の年表



Random Screening and Molecular Modification

Captopril

r-Insulin

Infliximab

Etanercept

Imatinib

We are here!

Drug Discovery by Design

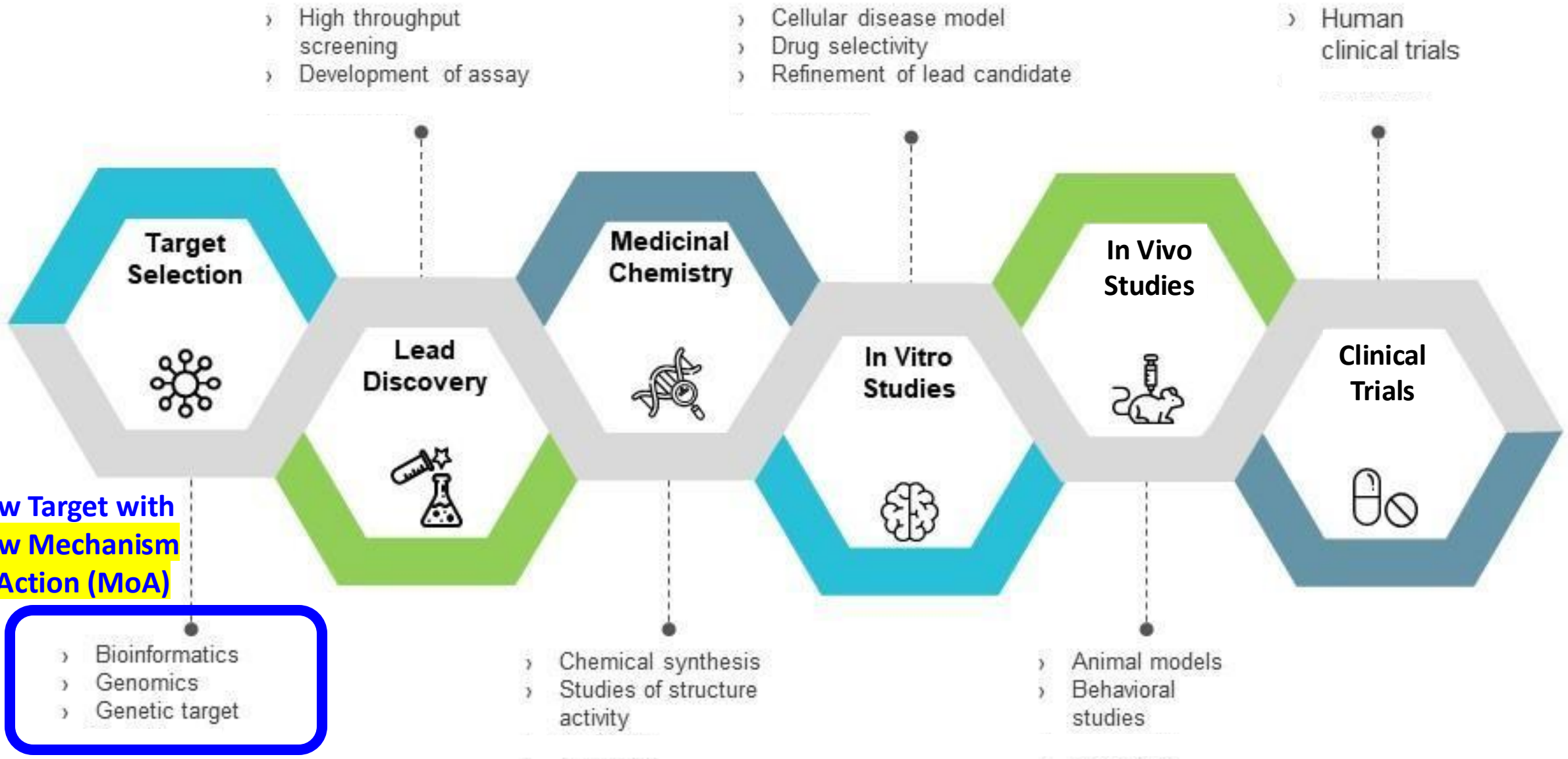
Gene Cloning and Molecular Targeting

Mechanism of action (MoA) comes first

and candidate substance follows.

https://www.cell.com/cell/fulltext/S0092-8674%2820%2930233-6

Recent Drug Development 最近の新医薬品開発



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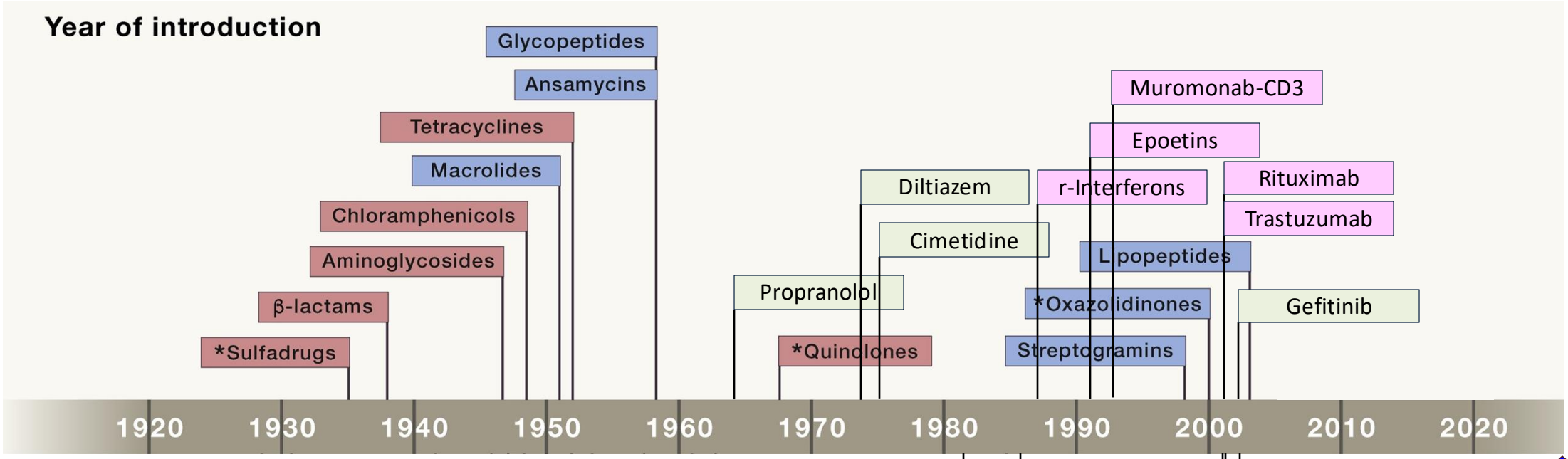

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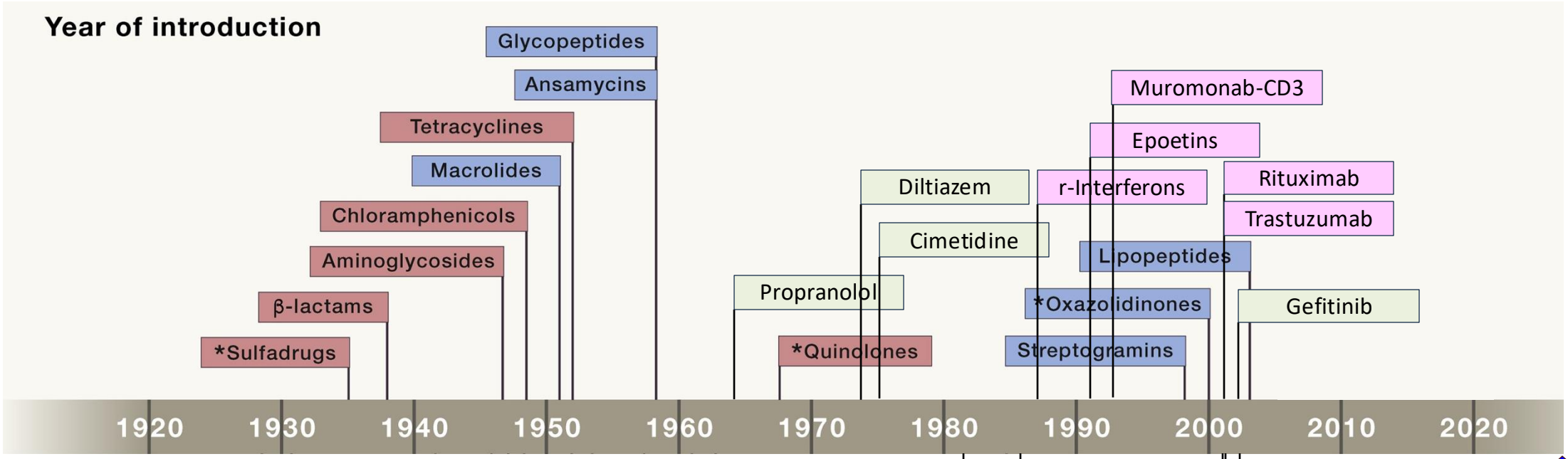

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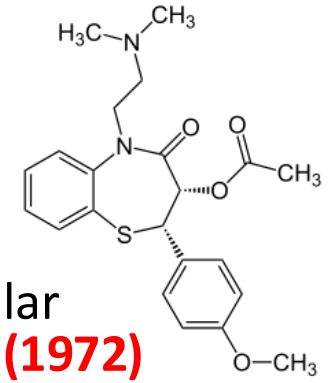
[Example] Development of Diltiazem Hydrochloride for angina pectoris and hypertension

【事例】: 塩酸ジルチアゼム（ヘルベッサー®，狭心症・高血圧症治療薬）の開発

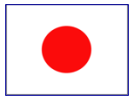
From random screening of 1,5-benzothiazepine derivatives



1. **Strong coronary vasodilation** in perfused guinea pig hearts **(1968)**
2. Increased coronary blood flow in anesthetized dogs
3. Selection of *d-cis* form (diltiazem) by isomeric activity comparison
4. **Calcium antagonist activity of diltiazem revealed** by perfused rabbit auricular artery, **despite unique chemical structure** unlike other calcium antagonists **(1972)**

   ⋮
5. Manufacturing authorization and markeing **in Japan (1973)**
6. Marketing authorization **in U.S. (1982**, the first cardiovascular drug invented in Japan to receive MA from the FDA)
7. **In the mid-1980s**, annual sales of **US$2 billion/year**, distributed in 70 countries

(→ The Pioneer of blockbusters from Japan)



led by
Prof. Taku Nagao (長尾 拓 博士)

Affiliation:
Tanabe Seiyaku Co., Ltd.
at the time
and later he served as Professor at the Univ. of Tokyo and Director General of the NIHS

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AND

OR

Double-Blind RCT

画期性加算

有用性加算

市場性加算

小児加算

先駆け加算

特定用途加算

Regenerative Medical Products
(Cell Therapy Products)
"Single-Arm Clinical Trial"
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ニュース解説

国内初の遺伝子治療薬「コラテジェン」薬価60万円は高いか安いか

更新日 2019/09/12

Japan's First Gene Therapy Product "Collategene"
Price: 600,000 JPY, high or low?
(Answers News 12 Sep 2019)

9月10日、国内初の遺伝子治療薬「コラテジェン」が発売されました。注目された薬価は1回60万円となりましたが、投資家に「安すぎる」と受け止められ、アンジェスの株価は急落。アンジェスは本承認後の加算に期待するとともに、収益化に向けて海外展開を急ぐ考えです。

INDEX

コラテジェンの薬価算定

算定方式	原価計算方式
製品総原価	43万7582円
	7万6615円（流通経費除く価格の14.9%）
	4万1692円（消費税除く価格の7.5%）
消費税	4万4471円
補正加算	なし
算定薬価	4mg1.6mL 1瓶　60万360円
市場規模予測	投与患者数992人/販売額12億円（ピーク時）

中医協総会（2019年8月28日）の資料をもとに作成

No premium was granted.

再生医療等製品の価格算定は、投与形態などの製品特性から医薬品に近いと判断されたものは薬価の算定方式に沿って、医療機器に近いと判断されたものは医療機器の算定方式に沿って行われることになっています。再生医療等製品に特化した価格算定の仕組みは、今のところありません。

コラテジェンは医薬品に近いと判断され、薬価は製造原価に企業の利益や流通経費を積み上げる「原価計算方式」で算定。しかし、画期的な治療薬であるにもかかわらず、それを評価する「画期性加算」や「有用性加算」はつきませんでした。そもそもコラテジェンは、ごく小規模の臨床試験の結果をもとに5年間の条件・期限付きで承認されており、今はいわば「仮免許」の状態。加算がつかなかった背景には、データが乏しく現時点では有効性の評価が限定的であるという事情があります。

https://answers.ten-navi.com/pharmanews/16896/

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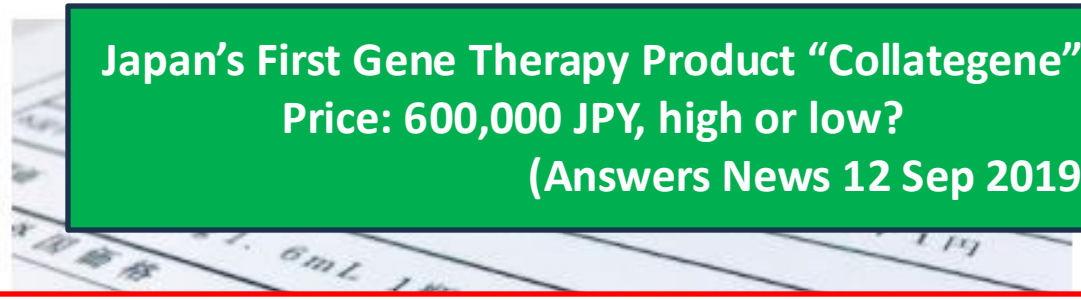

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Collategene is considered to be similar to a pharmaceutical product, and the drug price is calculated using the "cost accounting method," which adds the company's profit and distribution costs to the manufacturing cost. However, despite the fact that Collategene is an advanced therapeutic product, neither a "premium for innovativeness" nor a "premium for usefulness" was added to the drug price to take it into account. In the first place, based on the results of a very small clinical trial, Collategene was approved with a five-year condition and time limit, and is now in a state of "provisional license" so to speak. The reason why the premium was not granted is that the evaluation of efficacy is limited at this point due to a lack of data.

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- 加算のあり方 中医協が検討
- 収益最大化へ 米国開発急ぐ

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"Single-Arm Clinical Trial"
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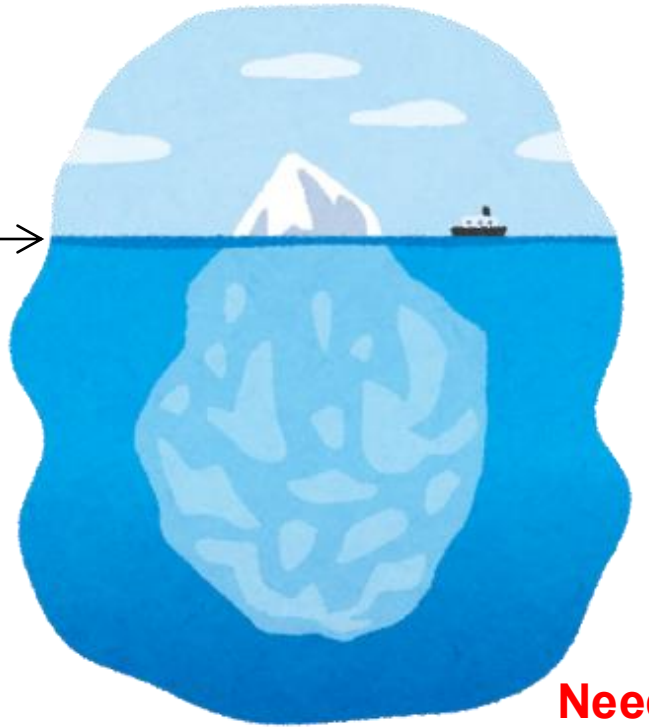
Cell Therapy Products are Complex
細胞加工製品は複雑

Limited Characterization Window
(Recognizable Quality Attributes)

Limit of Knowledge

Hidden/Unrecognizable
(but Potentially Critical)
Quality Attributes



Efficacy

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/ Inhomogeneity
不均質性／不均一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 inhomogeneity 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**不均一性を「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）**

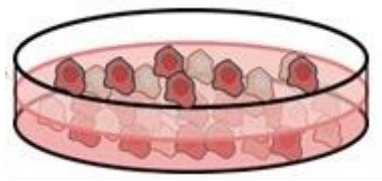
EXAMPLE (A)

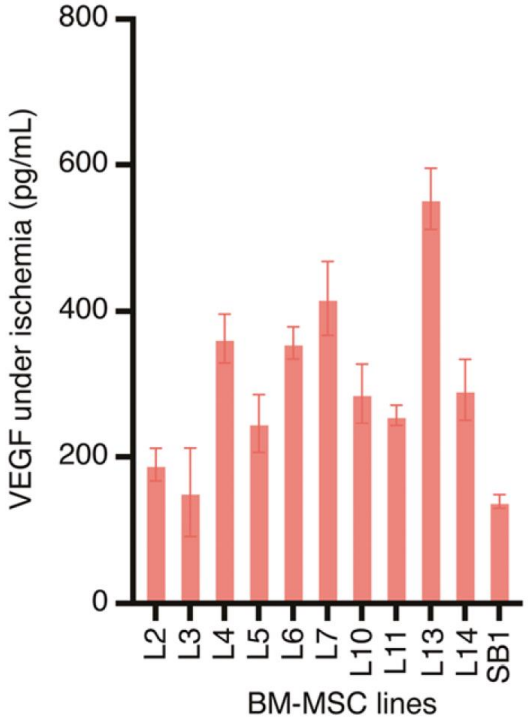
Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

Secretion of angiogenic factors under conditions that mimic the environment (ischemia) at the site of implantation

VEGF secretion under ischemic conditions

hBM-MSCs (PS#5)
Hypoxia
Glucose-free





VEGF
(vascular endothelial growth factor)

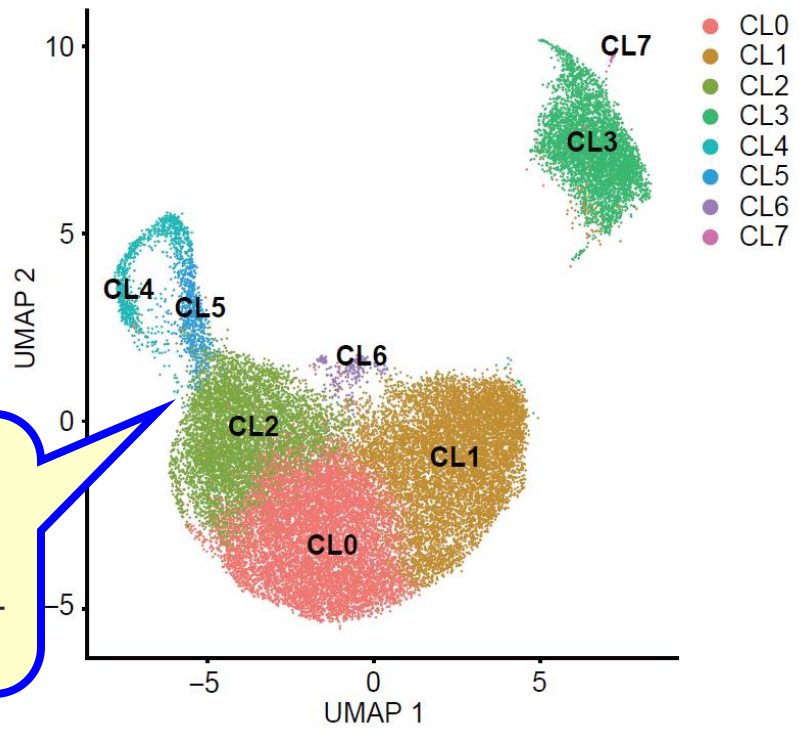
VEGF secretion is highly variable between cell lots.

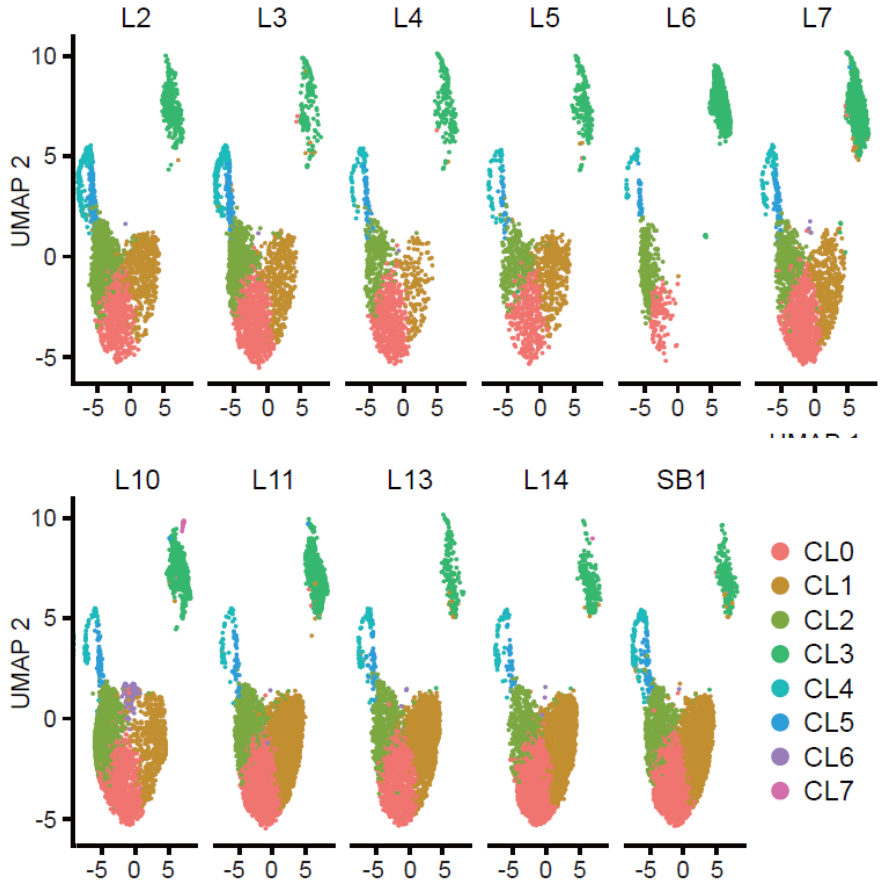
Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

Single-Cell Transcriptome Experiments

BM-MSCs (P5)
Normoxia

Integration and clustering of data from 11 lots of human bone marrow-derived MSCs



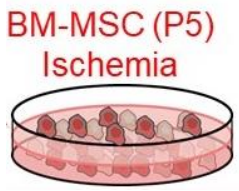


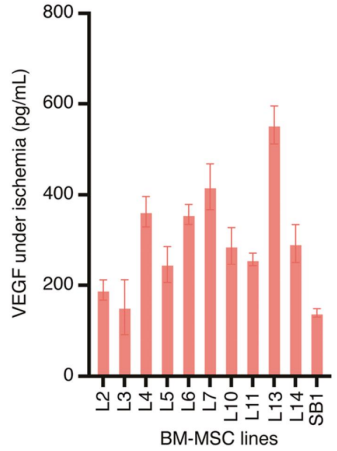
The population of bone marrow-derived MSCs was estimated to consist of 8 clusters

The degree to which the "inhomogeneity of each lot" deviates from the "inhomogeneity of the population" is visible.

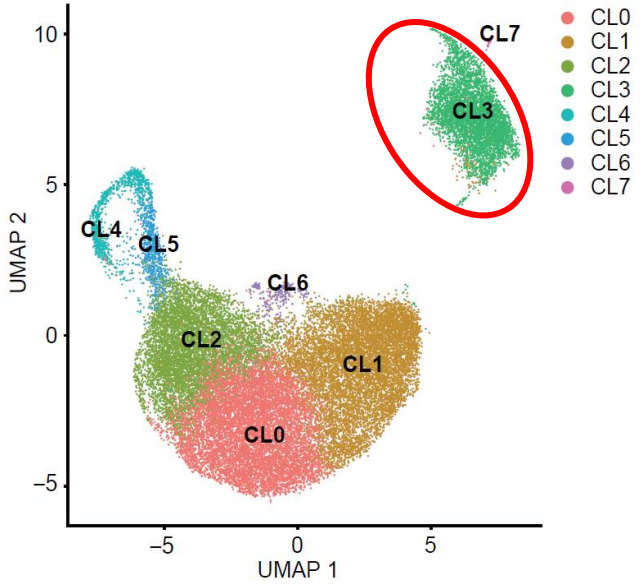
Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

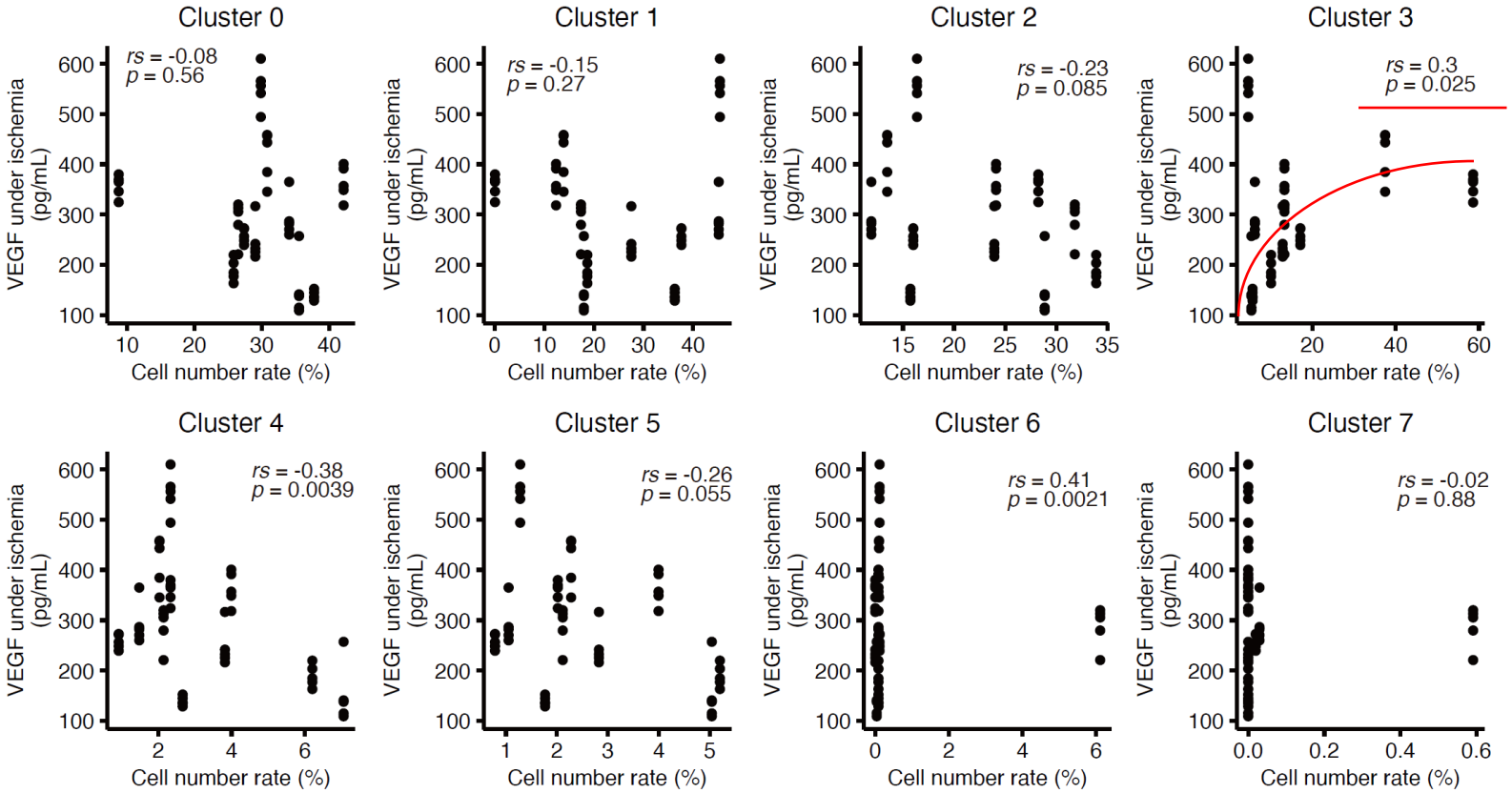
Single-Cell Transcriptome Experiments





BM-MSCs (P5)
Normoxia



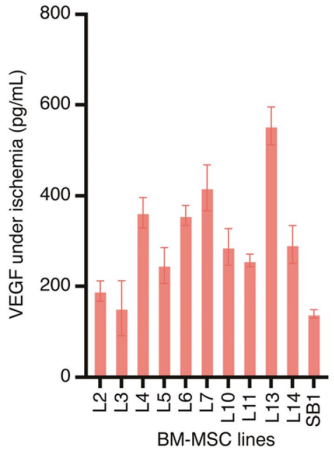


Miura T *et al., Stem Cells Transl Med.* 2023;**12**:379-390.

Functional involvement of LRRC75A

It is important to ensure this cell population, if you expect to reproduce angiogenesis and VEGF secretion!

BM-MSC (P5)
Ischemia



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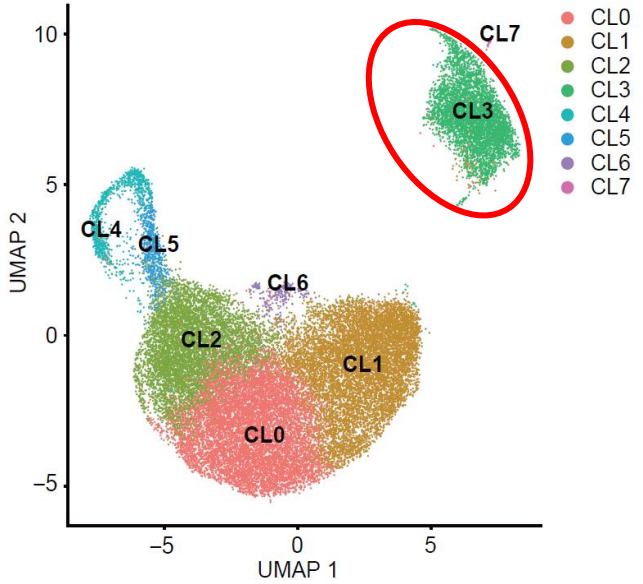
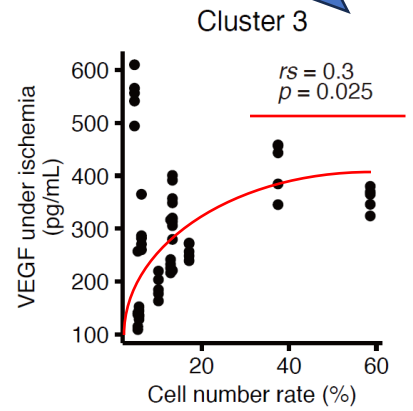


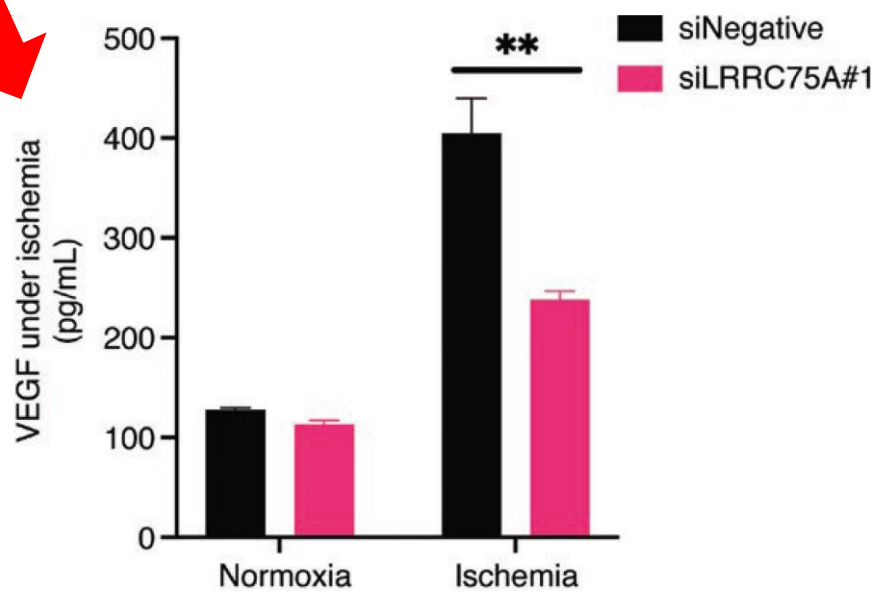
Top 20 upregulared genes of CL3

Gene name	Ave $\log_2$FC
LRRC75A	1.0357
KRT7	0.8382
KRT16	0.7902
C1orf56	0.7815
CRYAB	0.7696
HSPB1	0.7572
MTRNR2L12	0.7060
AC092069.1	0.7024
ADIRF	0.6712
LGALS1	0.6573
ID1	0.6525
MT2A	0.6424
S100A11	0.6312
COMP	0.6132
EIF5A	0.6057
FLG	0.6049
SH3BGRL3	0.5970
TPM2	0.5859
POLR2L	0.5555
GADD45B	0.5543

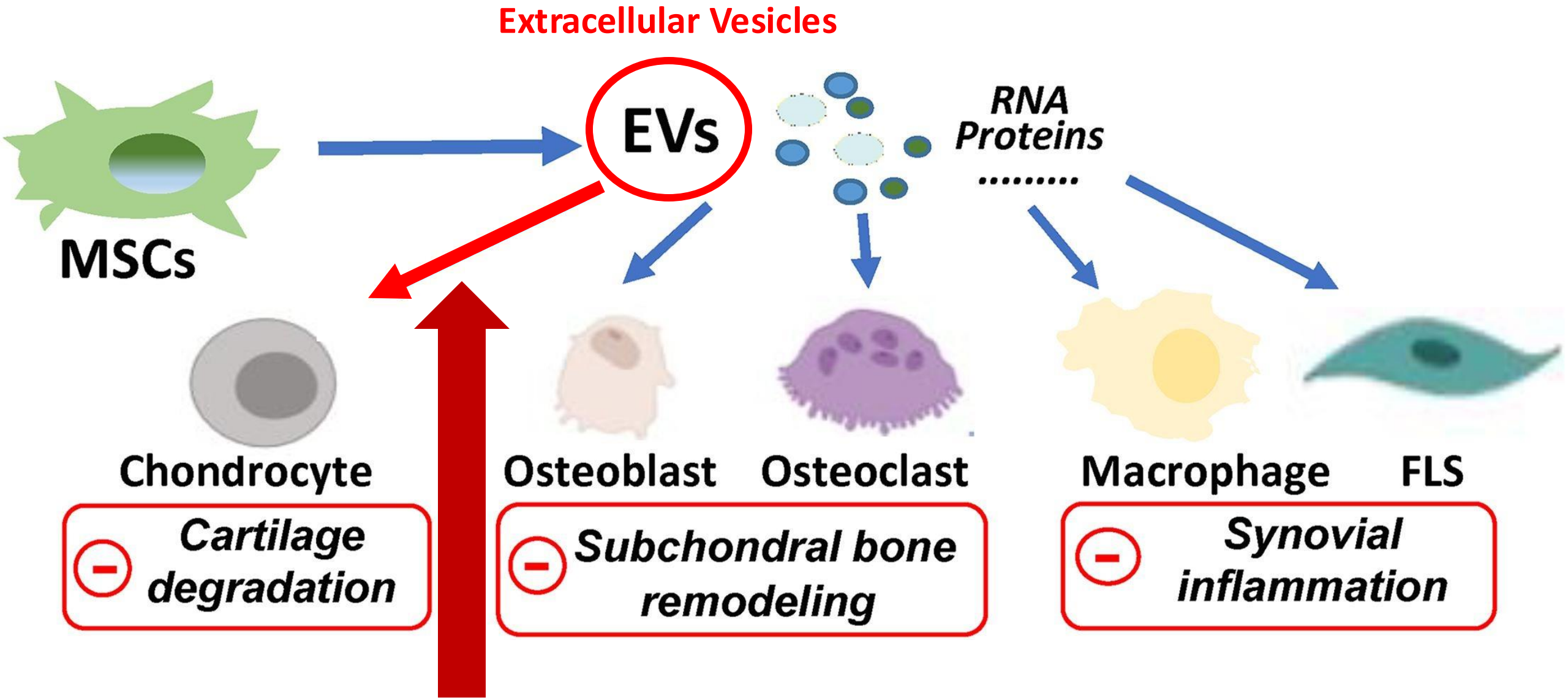
Hidden CQAs



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



EXAMPLE (B)



https://www.sciencedirect.com/science/article/pii/S0006295224002090

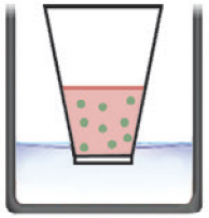
Chondrocyte Migration Assay (chemotaxis assay) to Evaluate the Chemotaxis-promoting Effect of hADSC-derived EVs

ClearView Chemotaxis Assay

1. Coat (migration) or prime (invasion) the insert

Prepare membrane surface for cell migration or invasion.

2. Harvest and seed (migration) or embed (invasion) cells

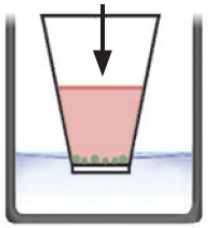


For migration, seed 1000-5000 cells and allow to settle.

For invasion, embed cells within matrix and centrifuge.

3. Treat cells

drug compound

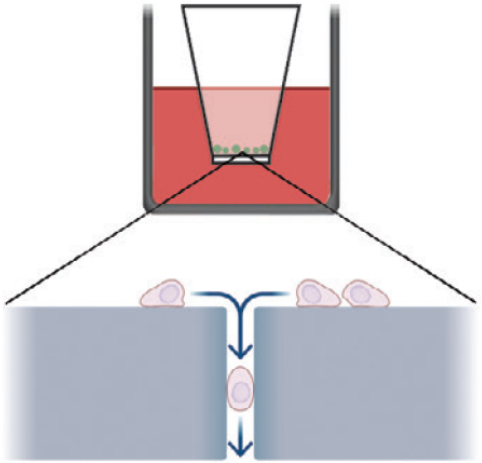


Add modulators of cell migration or invasion.

4. Add chemoattractant

Add chemoattractant or controls to reservoir plate wells.

5. Place in IncuCyte® and walk away



Automatically collect time-lapse images.

Observe cell morphology.

Quantify migration and invasion.

± EVs

Poster # P-07-01

https://www.sartorius.com/download/819566/cell-migration-and-invasion-assays-brochure-data.pdf

Effects of EVs derived from human adipose-derived MSCs (hADSCs) on the migratory activity of human chondrocytes

Unpublished data
論文未発表データ

Poster # P-07-01

Functional association between the effect of EVs and the hADSC clusters

The population size of Cluster F correlated significantly with the migration-promoting effect of the EVs on human chondrocytes.

It may be important to ensure cells of Cluster F, if you expect to reproduce the effect of hADSC-derived EVs on chondrocytes!

Unpublished data
論文未発表データ

Poster # P-07-01


Kanagawa Prefectural Government Office
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SHI KUHS Cyto-Facto KRM (Keio Univ.)
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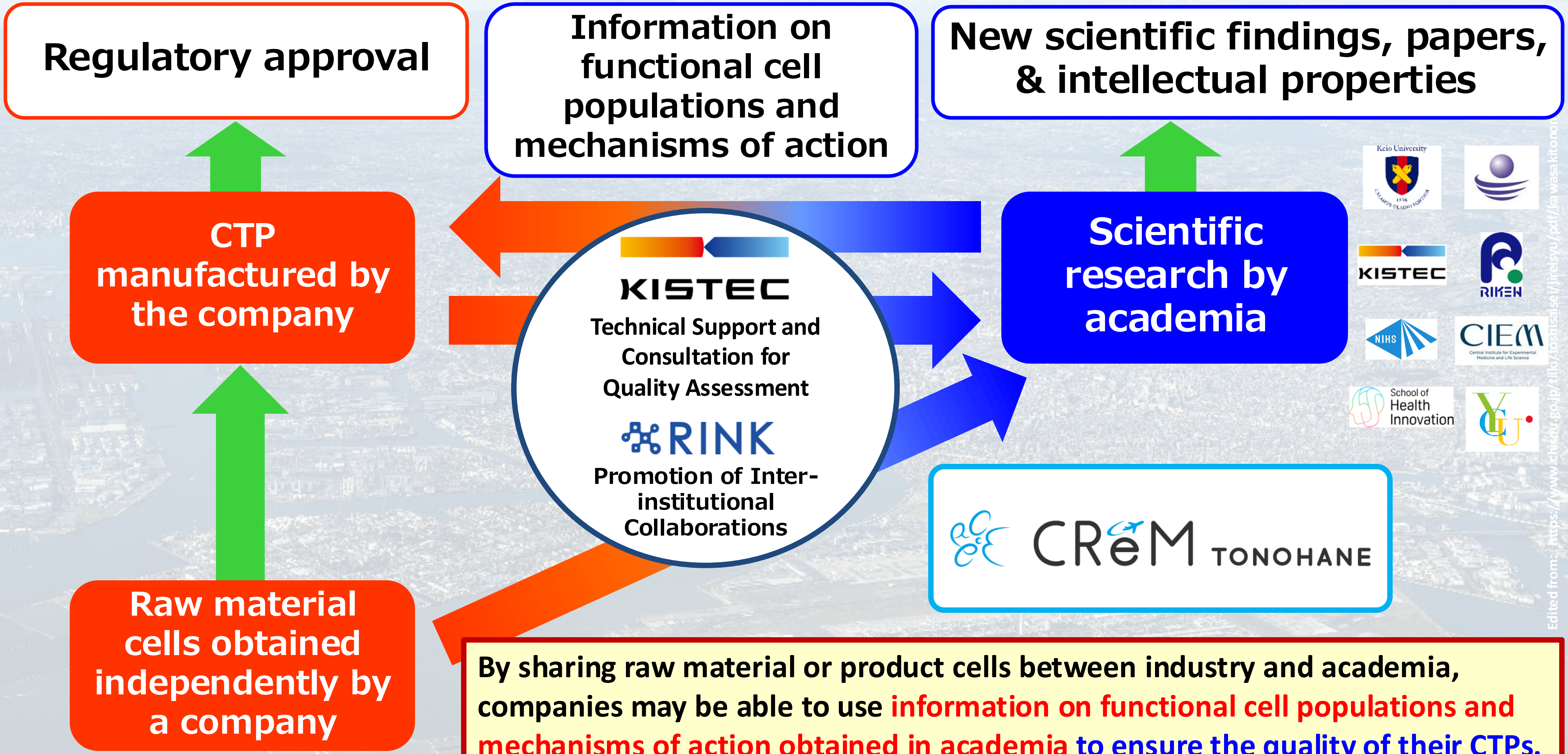
"Visualization" of heterogeneity/inhomogeneity and understanding of quality, mechanism of action, and product value of raw material cells and active ingredient cells



By sharing raw material or product cells between industry and academia, companies may be able to use **information on functional cell populations and mechanisms of action obtained in academia** **to ensure the quality of their CTPs.**
→ possibly leading to their product value and flexible cell manufacturing

“…, many people do not understand what the value is in the first place. If you don’t understand the value, the following happens: ”

“…、多くの人が「そもそも価値とは何か？」を理解していません。価値を理解していないと、次のようなことが起こります。”

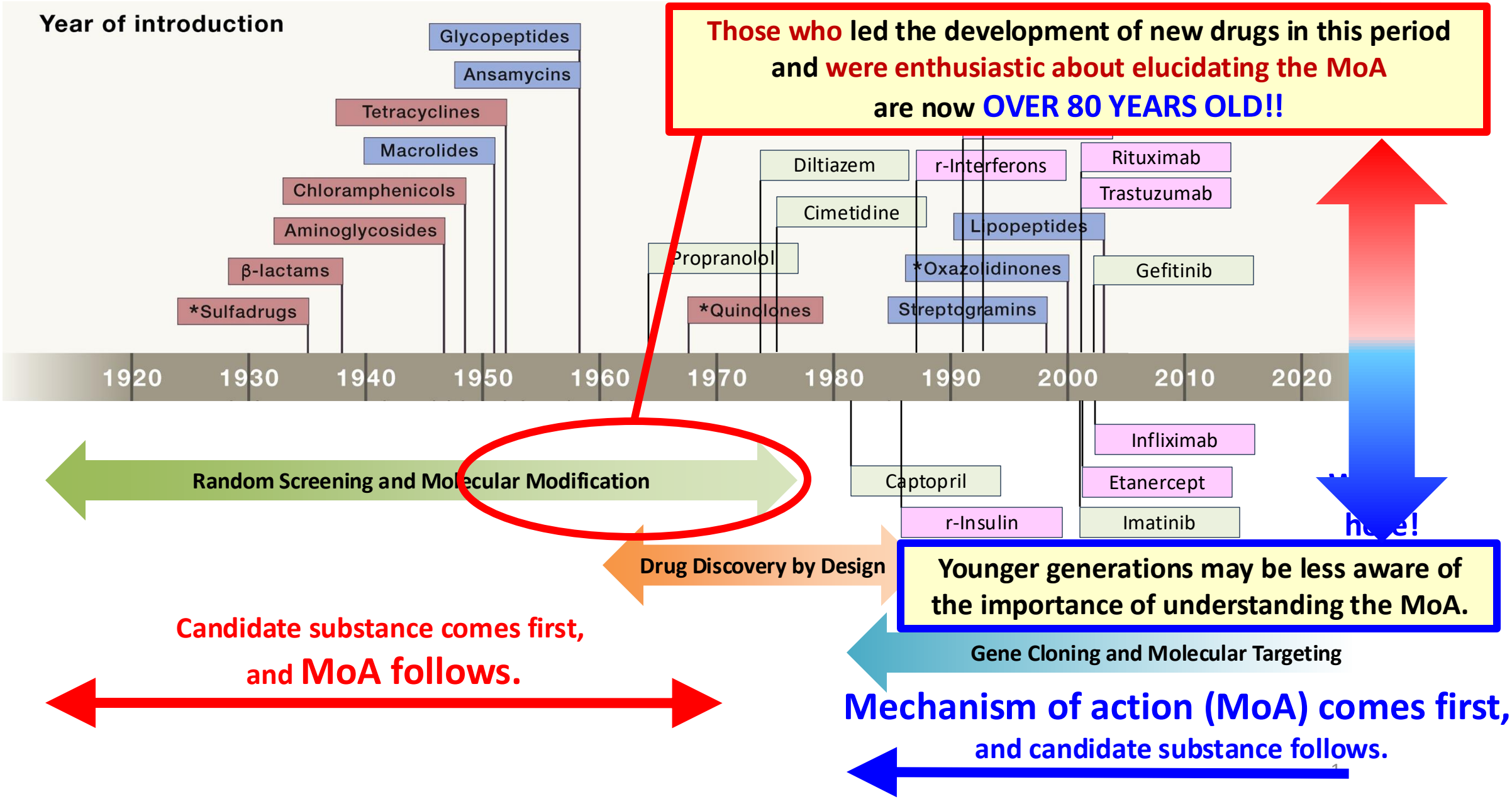
Nozomu TAJIRI（田尻 望, Representative Director & CEO of KAKUSHIN）

- 価値を理解していないから、そもそも価値をつくれない
- 偶然に価値をつくれたとしても、繰り返し再現できない
- 再現できないから、仕組みにできない
- 仕組みにできないから、システムにできない
- システムにできないから、自動化できない
- 自動化できないから、生産性が低い
- 生産性が低いから、報酬も低い

https://president.jp/articles/-/64232?page=2

- You don't understand the value, so you can’t make the value in the first place.
- Even if you could make it by chance, you would not be able to reproduce it repeatedly.
- Because you can’t reproduce it, you can’t make it into procedures.
- Because you can’t make it into procedures, you can't create a system.
- Because you can’t create a system, you can't automate it.
- Because you can't automate it, your productivity is low.
- Because your productivity is low, your rewards are also low.

The Timeline of Drug Discovery 主な創薬の年表

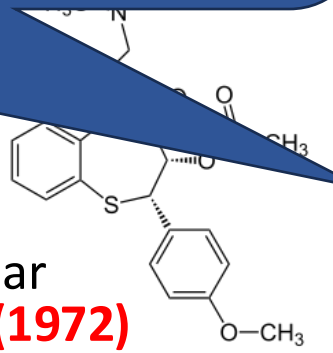


oride

の開発

"If it's a good drug that really works,
the pharmacology and mechanism of action will follow later."

「本当に効く良い薬であれば、薬理や作用機序は後から付いて来るんだよ」



1. **Strong coronary vasodilation** in perfused guinea pig hearts (1
2. Increased coronary blood flow in anesthetized dogs
3. Selection of *d-cis* form (diltiazem) by isomeric activity comparison
4. **Calcium antagonist activity of diltiazem revealed** by perfused rabbit auricular artery, **despite unique chemical structure** unlike other calcium antagonists **(1972)**

⋮

5. Manufacturing authorization and marketing **in Japan (1973)**
6. Marketing authorization **in U.S. (1982**, the first cardiovascular drug invented in Japan to receive MA from the FDA
7. In the mid-1980s, annual sales of **US$2 billion/year**, distributed in 70 countries

(→ The Pioneer of blockbusters from Japan)

led by
Prof. Taku Nagao (長尾 拓 博士)

Affiliation:
Tanabe Seiyaku Co., Ltd.
at the time
and later he served as Professor at the Univ. of Tokyo and Director General of the NIHS

ACKNOWLEDGMENTS

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For more information about the technical assistance/consultation by CReM TonoHane's Quality Evaluation Team for the quality evaluation of cell therapy products, please contact:

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