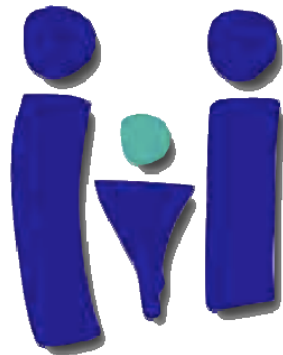


バイオロジクスフォーラム第9回学術集会

ヒトES細胞の臨床応用へ向けた取り組み

日時:平成24年2月22日
於 :タワーホール船堀



国立成育医療研究センター研究所
再生医療センター

阿久津英憲

ES細胞 期待と課題

体のさまざまな組織になれるヒト胚性幹細胞（ES細胞）を使った再生医療の臨床試験（治験）で、「目の病気が良くなった」という初の成果が米国で報告された。しかし症例数はわずかで、脊髄損傷の治験をしていた企業は経営上の理由で撤退。期待の高い再生医療だけに、実用化に向けて引き続き公的支援の必要性を指摘する声もある。

米アドバンスト・セル・テクノロジー（ACT）は1月、患者2人で視力の改善がみられたと発表した。「黄斑変性」（スタルガルト病）で治療を受けた50代女性は、目の前で手が動いているのが判別できる程度だったのが、視力表の文字をいくつか読めたといい、米メディアに「何年かぶりに針に糸を通してボタン付けができた」と喜びを語った。また「加齢性黄斑変性」の70代女性も「腕時計を見たら時間がわかって驚いた」と話した。

だが米紙ニューヨーク・タイムズによれば、70代女性は移植を受けていない方の目でも視力の改善がみられ、研究チームの責任者、カリフォルニア大学のステイブン・シュワルツ医師は「プラセボ（偽薬）効果

米治験で成果 一方で企業は撤退

かもしれない」と慎重だ。

一方、脊髄損傷によるまひの治験を行っていた米ジェロンは昨年11月、撤退を決めた。脊髄損傷の治療はもともと難しいと考えられており、ES細胞研究部門を売却する意向だが、話はまとまっていない。ただジェロンは治験で「深刻な副作用は見つかっていない」とし、ACTの治験でも細胞のがん化などは確認されず、安全性の手がかりは得られた。

国立成育医療研究センター研究所の梅沢明弘副所長は、ジェロンの治験を「安全性をある程度証明しただけでも十分意味はあった」と評価する。「むしろ、ES細胞が治療に使える可能性は高まった」と話す。

ES細胞と同じくどんな組織にもなれるiPS細胞を開発した京都大学の山中伸弥教授は、これらを使う再生医療は全く新しいものであることから、「当初からビジネスとして成功させるのはかなり困難」とみる。「すぐに利益がなくても試験を続けられる体制づくりが必要だ」とも話し、継続的な公的支援の必要性を訴える。

（行方史郎・ワシントン、鍛冶信太郎）

本日の内容

1. **ヒトES細胞の臨床試験の現況**
2. **臨床応用を目指すヒトES細胞樹立の技術的要件**

本日の内容

1. ヒトES細胞の臨床試験の現況
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Geron社による取り組み

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Safety Study of GRNOPC1 in Spinal Cord Injury

This study is currently recruiting participants.

Verified on October 2011 by Geron Corporation

First Received on October 6, 2010. Last Updated on October 26, 2011 [History of Changes](#)

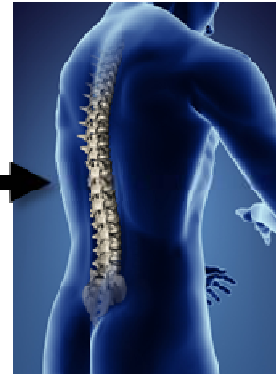
Sponsor:	Geron Corporation
Information provided by (Responsible Party):	Geron Corporation
ClinicalTrials.gov Identifier:	NCT01217008

Purpose

The purpose of the study is to evaluate the safety of GRNOPC1 administered at a single time-point between 7 and 14 days post injury, inclusive, to patients with neurologically complete spinal cord injuries (SCI).

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Spinal Cord Injury	Biological: GRNOPC1	Phase I

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment



San Francisco Chronicle “Geron Presents Clinical Data Update From GRNOPC1 Spinal Cord Injury Trial ”

Phase 1 Clinical Trial Data

Data were presented on four patients with neurologically complete American Spinal Injury Association (ASIA) Impairment Scale grade A thoracic spinal cord injuries, who received GRNOPC1 at a dose of two million cells delivered by injection into the lesion site using a syringe positioning device designed by Geron. GRNOPC1 was administered between 7 and 14 days after injury. Low-dose tacrolimus was given for temporary immune-suppression from the time of injection for 46 days, at which point the dose was tapered and withdrawn completely at 60 days.

Endpoints of the trial are safety and evaluation of neurological function, using standardized testing at specified timepoints to monitor sensory and lower extremity motor function. The trial protocol also includes multiple MRI scans. Initial follow-up of patients is one year. One patient in the trial has completed the Day 365 follow-up visit. The most recent patient to be enrolled in the clinical trial has completed the Day 30 follow-up. After one year the patients enter a period of long-term follow-up that includes annual in-person visits for the first five years and subsequent yearly check-ups via telephone for an additional nine years.

Safety data to date from the trial has shown:

- No surgical complications during or after the procedures.
- No adverse events related to the injection procedures or to GRNOPC1.
- A few mild adverse events related to tacrolimus.
- No evidence of cavitation in the spinal cord at the injury sites on MRI.
- No unexpected neurological changes.
- No evidence of immune responses to GRNOPC1.

GRNOPC1 was delivered to four spinal cord injured patients at a dose of two million cells without complications from either the cells or the surgical procedure itself, and without any negative effects on the spinal cord or neurological function of the patients to date. The only side-effects observed were due to the immunosuppressive drug tacrolimus, which is administered for the first two months after injection of GRNOPC1. Furthermore, there is no evidence to date of immune rejection of GRNOPC1, an allogeneic cell therapy, including after withdrawal of immunosuppressive drug.

GRNOPC1 臨床試験の経過(2011年10月)

胸椎損傷-ASIA, Grade A
18~65歳
受傷後7-14日に細胞移植
GRNOPC1; 2×10^6



4症例 (#1; has completed the Day 365 follow-up visit, #2~; have completed the Day 30 follow-up visit)

安全性に関する影響

- なし→手術による合併症、
細胞移植による合併症
移植部位の変化(MRIによる観察)
移植免疫反応
移植による想定外の神経学的症状

- あり→タクロリムスによるもの
(マイナー)

(Oct. 20th, 2011)

Geron社がヒトES細胞臨床開発から撤退

“米Geron社、資金難でヒトES細胞の臨床開発を放棄、事業売却へ、38%の従業員を解雇”

(日経バイオテク , 2011年11月16日)

“Geron halting stem cell research, laying off staff”

(USA TODAY, 2011年11月15日)

“Geron abandons stem cell therapy as treatment for paralysis”

US biotech company Geron blames economic conditions for its decision to abandon the first-ever human trial of its kind

(thegurdian, 2011年11月15日)



(abc NEWS, 2011年11月16日)

Advanced Cell Technology, Inc.(ACT)社 のヒトES細胞臨床試験



<http://www.advancedcell.com/>

若年性遺伝性黄斑ジストロフィー症(シュタルガルト病)

Sub-retinal Transplantation of hESC Derived RPE(MA09-hRPE)Cells in Patients With Stargardt's Macular Dystrophy

This study is currently recruiting participants.

Verified on May 2011 by Advanced Cell Technology

First Received on April 28, 2011. Last Updated on May 16, 2011 [History of Changes](#)

Sponsor:	Advanced Cell Technology
Information provided by:	Advanced Cell Technology
ClinicalTrials.gov Identifier:	NCT01345006

Purpose

This is a safety and tolerability trial to evaluate the effect of subretinal injection of human embryonic stem cell derived retinal pigment epithelium cells in patients with Stargardt's Macular Dystrophy (SMD).

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Stargardt's Macular Dystrophy	Biological: MA09-hRPE Cellular therapy	Phase I Phase II

Study Type: Interventional
Study Design: Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Open Label

Official Title: A Phase I/II, Open-Label, Multi-Center, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem Cell Derived Retinal Pigmented Epithelial (MA09-hRPE) Cells in Patients With Stargardt's Macular Dystrophy (SMD)



Drs. Steven Schwartz and Robert Lanza

July 12, 2011: First Patients in each trial were treated by Dr. Steven Schwartz, M.D at Jules Stein Eye Institute (UCLA)

萎縮型加齢黄斑変性症

Safety and Tolerability of Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients With Advanced Dry Age Related Macular Degeneration (Dry AMD)

This study is currently recruiting participants.

Verified on April 2011 by Advanced Cell Technology

First Received on April 28, 2011. No Changes Posted

Sponsor:	Advanced Cell Technology
Information provided by:	Advanced Cell Technology
ClinicalTrials.gov Identifier:	NCT01344993

Purpose

This is a safety and tolerability trial to evaluate the effect of subretinal injection of human embryonic stem **cell** derived **retinal pigment epithelium cells** in patients with dry Age Related Macular Degeneration (AMD) and to perform exploratory evaluation of potential efficacy endpoints to be used in future studies **retinal pigment epithelium (RPE) cellular** therapy.

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Dry Age Related Macular Degeneration	Biological: MA09-hRPE Cellular Therapy	Phase I Phase II

Study Type: Interventional
 Study Design: Endpoint Classification: Safety Study
 Intervention Model: Single Group Assignment
 Masking: Open Label

Official Title: A Phase I/II, Open-Label, Multi-Center, Prospective Study to Determine the Safety and Tolerability of Sub-retinal Transplantation of Human Embryonic Stem **Cell** Derived Retinal Pigmented Epithelial (MA09-hRPE) **Cells** in Patients With **Advanced** Dry AMD



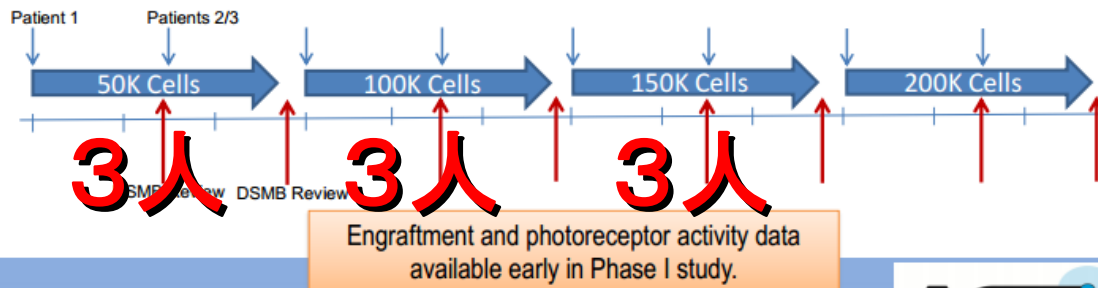
July 12, 2011: First Patients in each trial were treated by Dr. Steven Schwartz, M.D at Jules Stein Eye Institute (UCLA)

Phase I - Clinical Trial Design

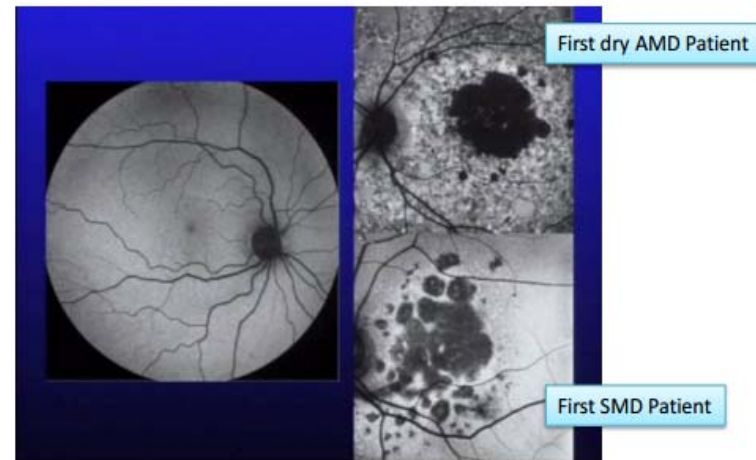
- 12 Patients for each trial, ascending dosages of 50K, 100K, 150K and 200K cells.
 - For each cohort, 1st patient treatment followed by 6 week DMSB review before remainder of cohort.
- Patients are monitored - *including high definition imaging of retina*

Permit comparison of RPE and photoreceptor activity before and after treatment

High Definition Spectral Domain Optical Coherence Tomography (SD-OCT)
Retinal Autofluorescence



ACT社による取り組み



臨床試験患者(2名)の眼底写真

RPE Program Summary

- Stargardt's (SMD) Disease
 - IND **approved** in November 2010
 - European CTA Approved – *enrolling patients*
 - Orphan Drug Designation granted in U.S. and Europe
 - *The SMD patient is a 26 year old female with baseline best corrected visual acuity of hand motion that corresponded to 0 letters in the ETDRS chart.*
- Dry AMD
 - IND **approved** in December 2010
 - European CTA in preparation
 - *The dry AMD patient is a 77 year old female with baseline BCVA of 20/500, that corresponded to 21 letters in the ETDRS chart.*



July 12, 2011: First Patients in each trial were treated by Dr. Steven Schwartz, M.D at Jules Stein Eye Institute (UCLA)



細胞移植デバイスと移植

ACT社ホームページより

<http://www.advancedcell.com/>



Embryonic stem cell trials for macular degeneration: a preliminary report

Steven D Schwartz, Jean-Pierre Hubschman, Gad Heilwell, Valentina Franco-Cardenas, Carolyn K Pan, Rosaleen M Ostrick, Edmund Mickunas, Roger Gay, Irina Klimanskaya, Robert Lanza

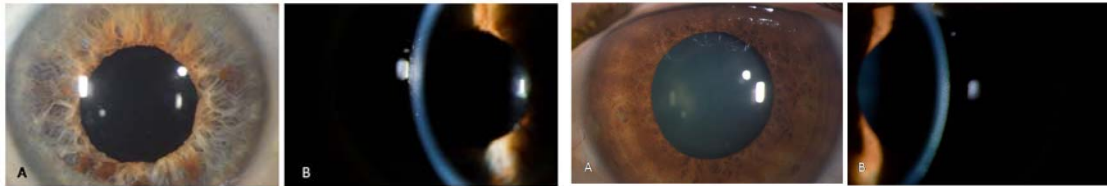
Summary

Background It has been 13 years since the discovery of human embryonic stem cells (hESCs). Our report provides the first description of hESC-derived cells transplanted into human patients.

Slit lamp images: 1 week post ope

AMD

Stargardt Disease



(The Lancet, Early Online Publication, 24 January 2012)

	BCVA	ETDRS (number of letters)
Fellow eye		
Baseline	Hand motion	0
1 week	Hand motion	0
2 weeks	Hand motion	0
3 weeks	Hand motion	0
4 weeks	Hand motion	0
6 weeks	Hand motion	0
8 weeks	Hand motion	0
12 weeks	Hand motion	0
Operated eye		
Baseline	Hand motion	0
1 week	Counting fingers	0
2 weeks	Counting fingers	1
3 weeks	Counting fingers	3
4 weeks	20/800	5
6 weeks	20/800	5
8 weeks	20/800	5
12 weeks	20/800	5

hESC=human embryonic stem cells. RPE=retinal pigment epithelium. BCVA=best corrected visual acuity. ETDRS=Early Treatment Diabetic Retinopathy Study visual acuity chart.

Table: Change in visual acuity after hESC-RPE transplantation in patient with Stargardt's macular dystrophy

"Embryonic stem cells improve vision for two women"



Dr. Steven Schwartz and a 51-year-old patient who says her vision has improved after stem cell treatment.

The second patient in the study, a 51-year-old woman who preferred not to use her name, said she first noticed a change in her vision a few weeks after surgery when she woke up one morning and looked at an armoire across her bedroom.

"It has a lot of detailed carvings and I thought wow, I was missing those before," she said. "I thought, is this for real?"

Later, she noticed she could see the knobs on her stove, which she couldn't see before at a certain distance.

2人目の女性(51)は手術から2~3週間たった朝、目覚めた時に寝室のたんすの細かい彫刻に気付き、視力の改善を実感したという。以前は見えなかったこんろのつまみが見えるようになり、目の前に示された指の数も分かるようになった。

(CNN, 24 January 2012)

若年性遺伝性黄斑ジストロフィー症(シュタルガルト病)
3症例の移植手術済み→第1コホート終了

**ACT Announces Third Patient with Stargardt's Disease Treated in U.S.
Clinical Trial with RPE Cells Derived from Embryonic Stem Cells**

Final Patient from First Cohort in Phase I/II Trial Using hESC-Derived RPE Cells

(2012年2月13日)

若年性遺伝性黄斑ジストロフィー症(シュタルガルト病)
ヨーロッパでも1症例

**ACT Announces Europe's First Human Embryonic Stem Cell Transplant
in Patient with Stargardt's Disease**

Moorfields Eye Hospital in London Initiates Clinical Trial Using hESC-derived RPE cells

(2012年1月23日)

ACT臨床試験(Dry AMD, SMD)がウィルズ・アイ・ホスピタルで承認

Leading Eye Institute to Participate in ACT's Embryonic Stem Cell Clinical Trial for Macular Degeneration

Wills Eye Institute receives IRB approval to treat dry-AMD using ACT's hESC-derived retinal pigment epithelial (RPE) cells

ACT Announces Approval of Wills Eye Institute as Additional Site for Stem Cell Clinical Trial for Stargardt's Disease

Leading Eye Institute Will Participate as Site for Both of ACT's Phase I/II Clinical Trials Using Human Embryonic Stem Cell-Derived RPE Cells for Macular Degeneration

ACT臨床試験(SMD)がスコットランドで承認

ACT Announces Aberdeen Royal Infirmary in Scotland as Additional Site for Phase 1/2 Clinical Trial Using hESC-Derived RPE Cells for Macular Degeneration

Second Site for First Human Embryonic Stem Cell Trial in Europe

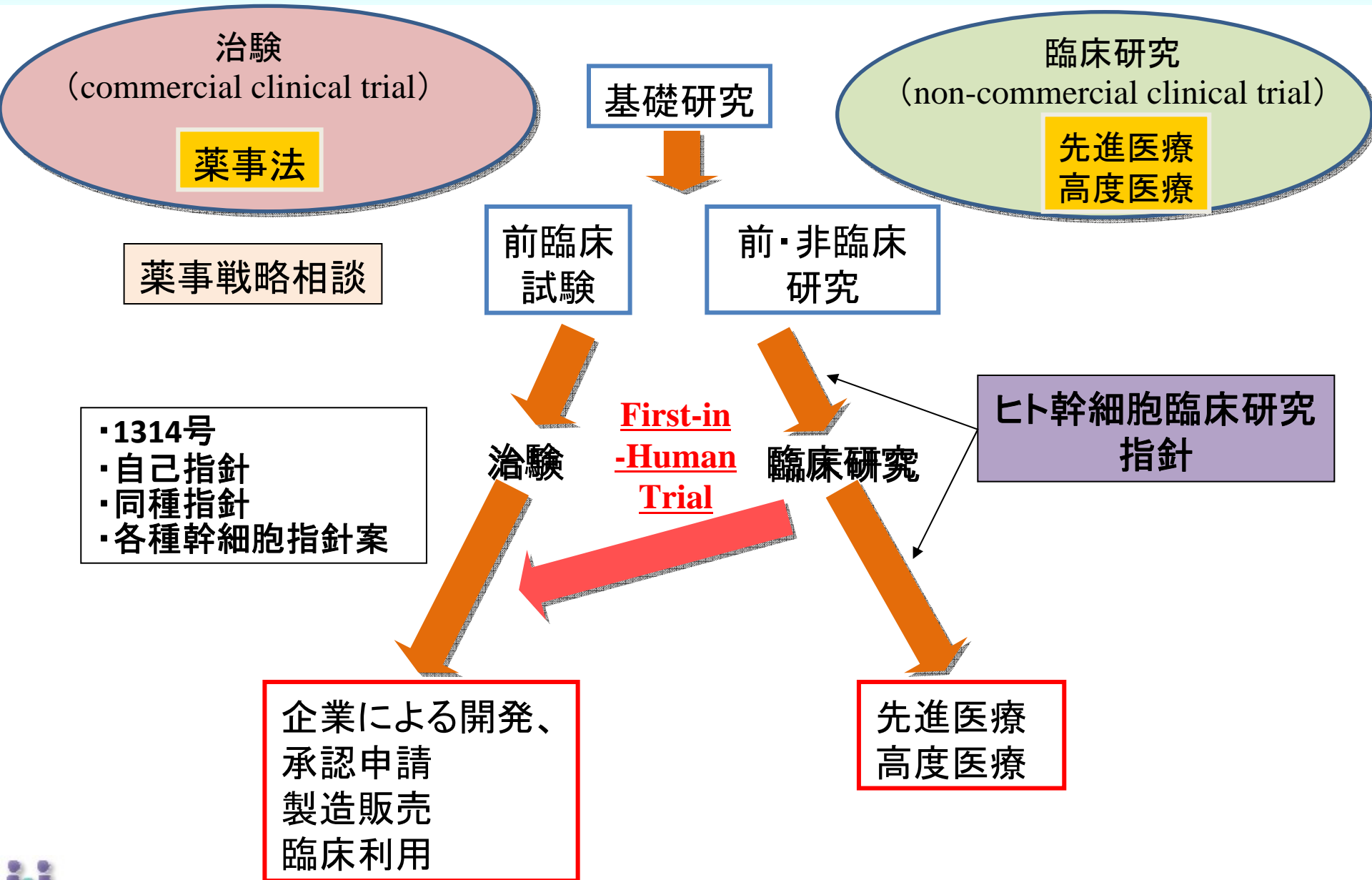
ACT社ホームページより

<http://www.advancedcell.com/>

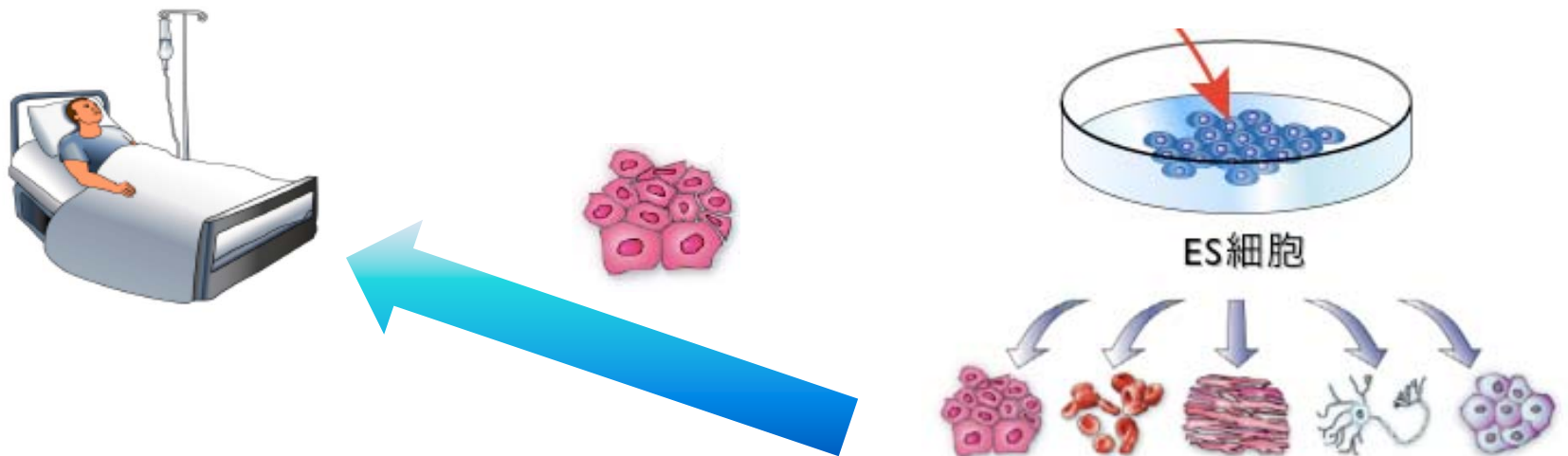
日本

再生医療への仕組み

再生医療研究の実用化への出口(日本)



ヒトES細胞による臨床応用



ヒトES細胞による臨床応用



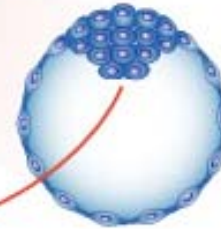
受精卵



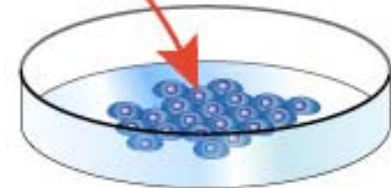
桑実胚



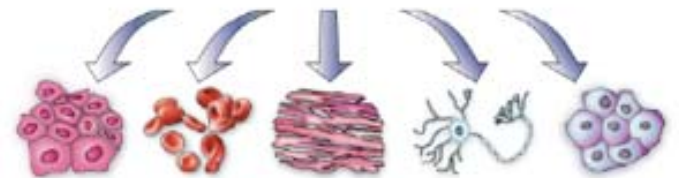
胚盤胞



内細胞塊



ES細胞



厚生労働省

倫理

安全

文部科学省

倫理

ヒトES細胞研究(日本)

文部科学省

基礎研究

- ・ヒトES細胞の使用に関する指針

使用すること

- ・ヒトES細胞の樹立及び分配に関する指針

樹立すること



文部科学大臣の確認

文部科学省

特定胚及びヒトES細胞等専門委員会

厚生労働省

臨床応用

使用すること

樹立すること



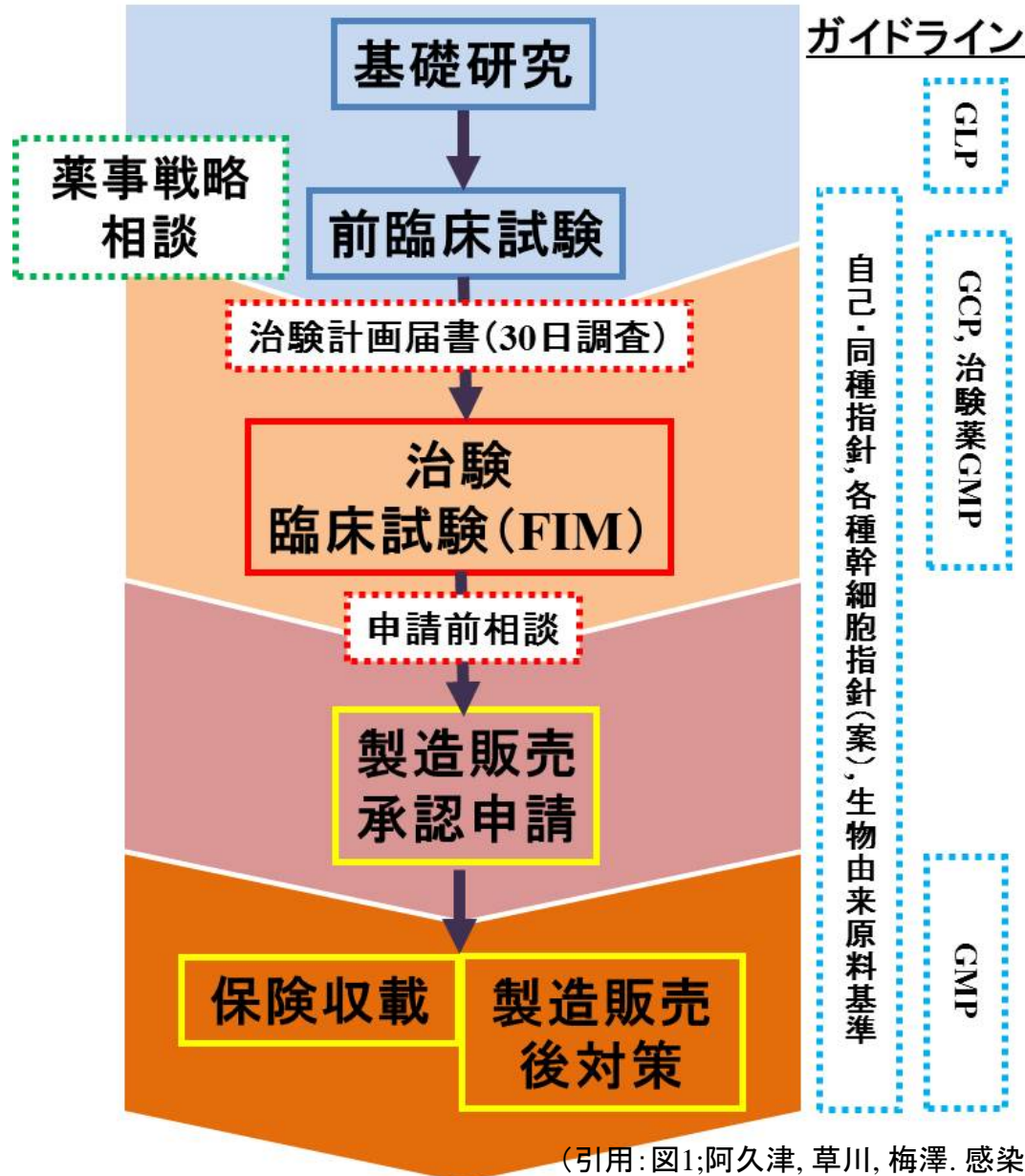
医師法

- ・ヒト幹細胞を用いる臨床研究に関する指針
(平成22年11月1日改正)

薬事法

- ・ヒトES細胞加工医薬品等の品質及び安全性の確保に関する指針(案)
(平成22年1月1日中間報告版)

細胞・組織利用医薬品の開発(日本)



本日の内容

1. **ヒトES細胞の臨床試験の現況**
2. **臨床応用を目指すヒトES細胞樹立の技術的要件**

本日の内容

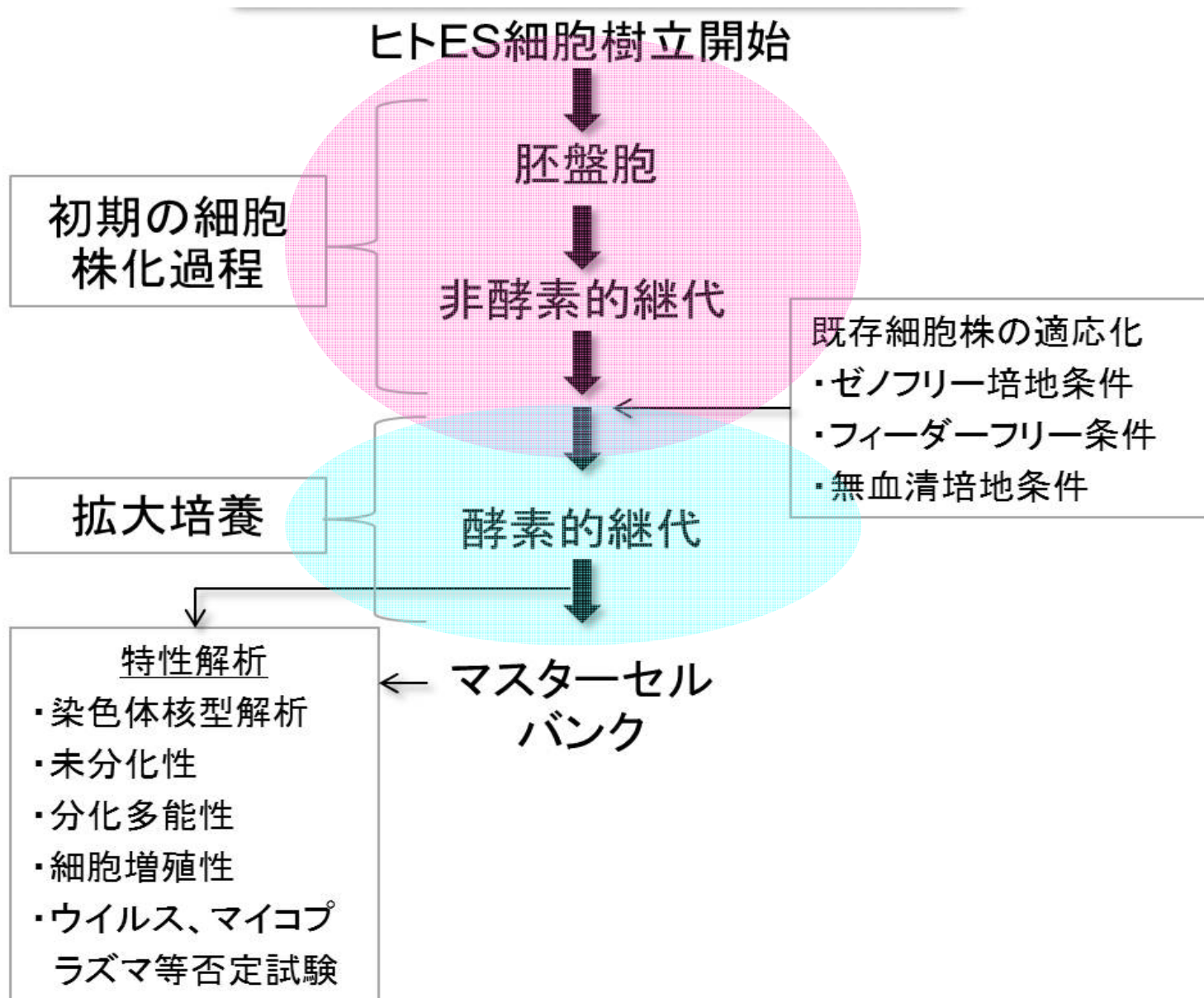
1. ヒトES細胞の臨床試験の現況
2. **臨床応用を目指すヒトES細胞樹立の技術的要件**

ヒトES細胞による臨床試験の要件

1. 安全性や品質の担保

2. 治療法の有効性を示す

ヒト多能性幹細胞の樹立から培養維持



ヒト多能性細胞の医療応用に必要な技術的要件

- ① 均一な細胞性質を保つ培養工程の確立
- ② 細胞の品質基準と管理体制の確立
- ③ 長期培養工程における細胞品質の管理と評価方法の確立
- ④ 動物由来成分の排除、感染性因子混入リスク管理

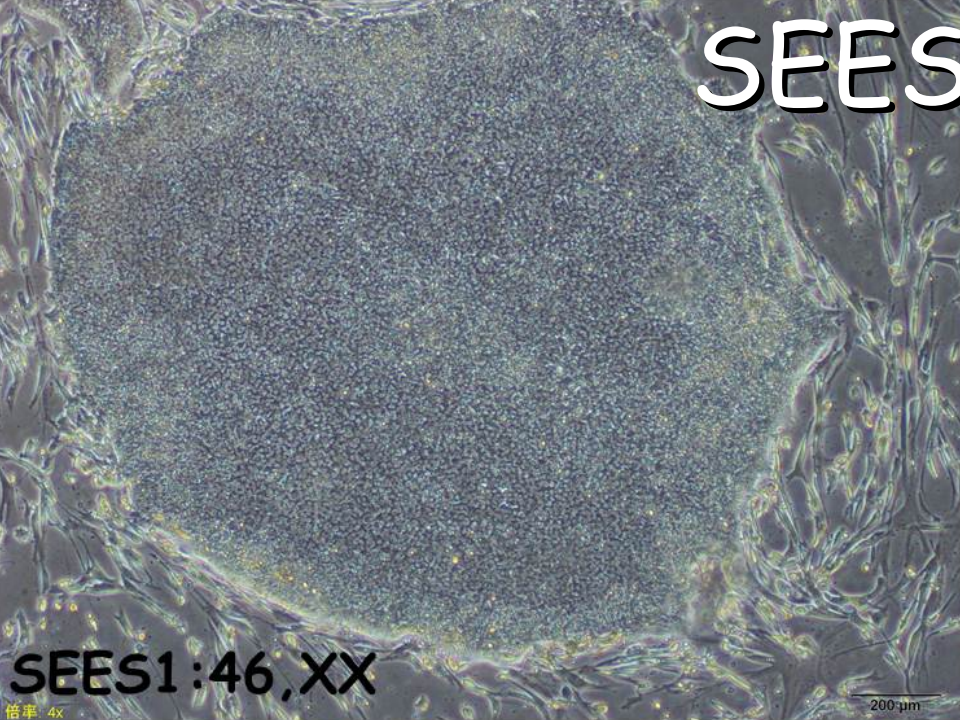
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国立成育医療研究センター
ヒトES細胞の樹立

SEIRES

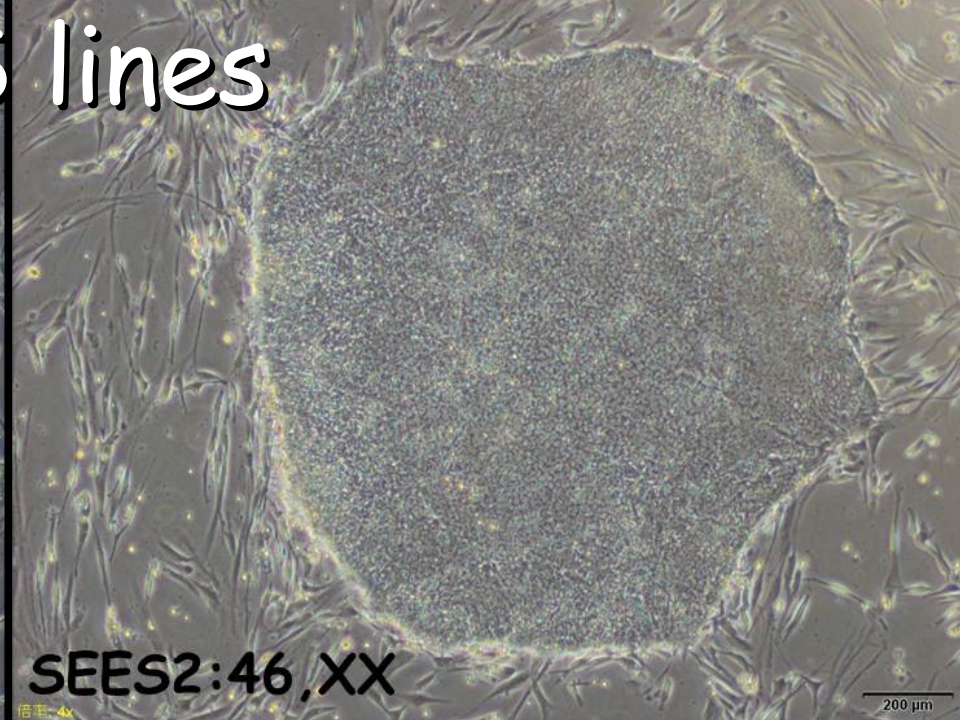
SEES lines



SEES1:46,XX

倍率: 4x

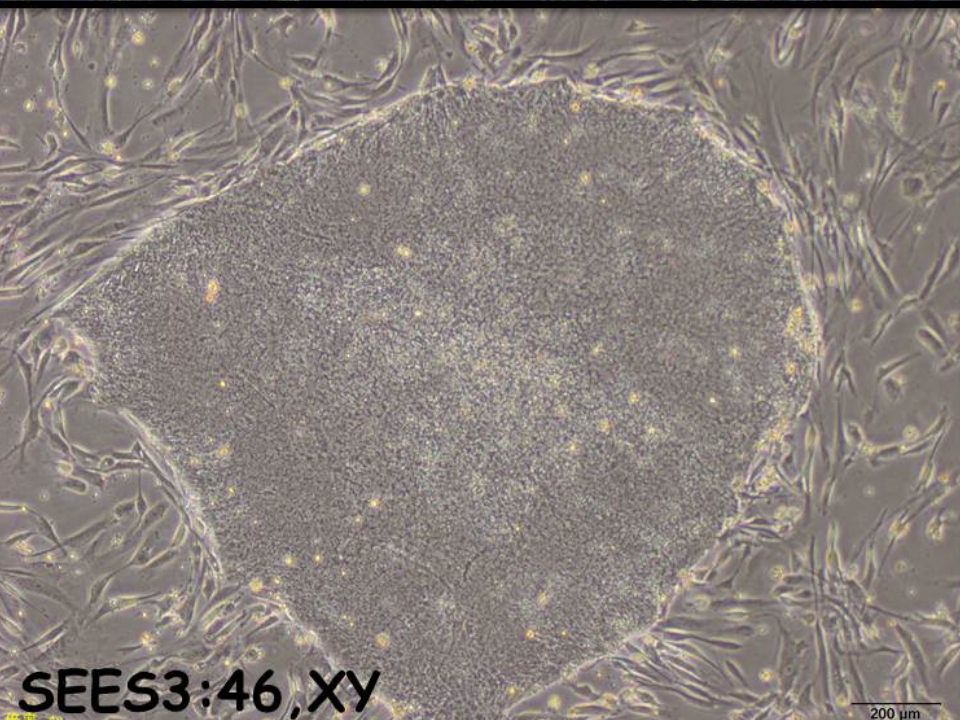
200 μm



SEES2:46,XX

倍率: 4x

200 μm

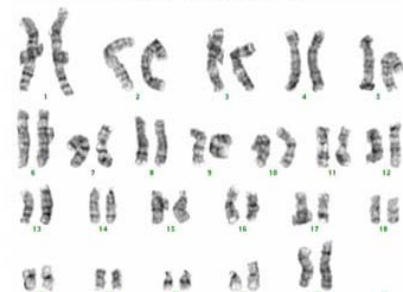


SEES3:46,XY

倍率: 4x

200 μm

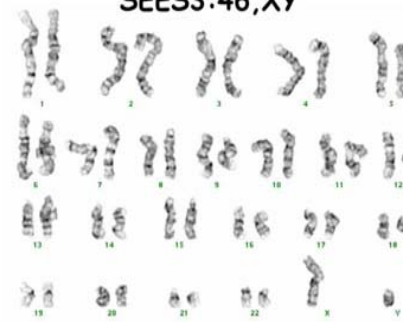
SEES1:46,XX



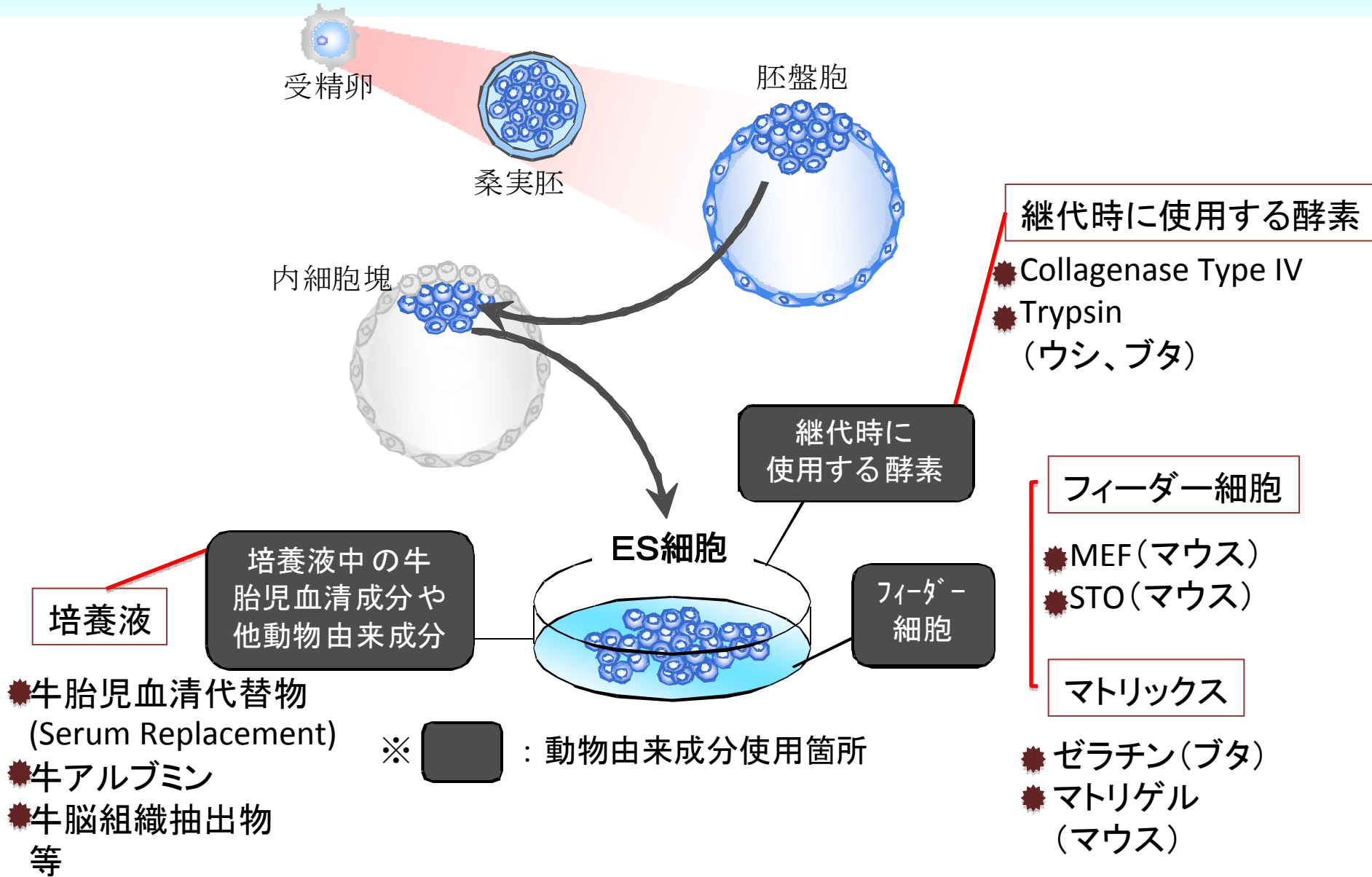
SEES2:46,XX

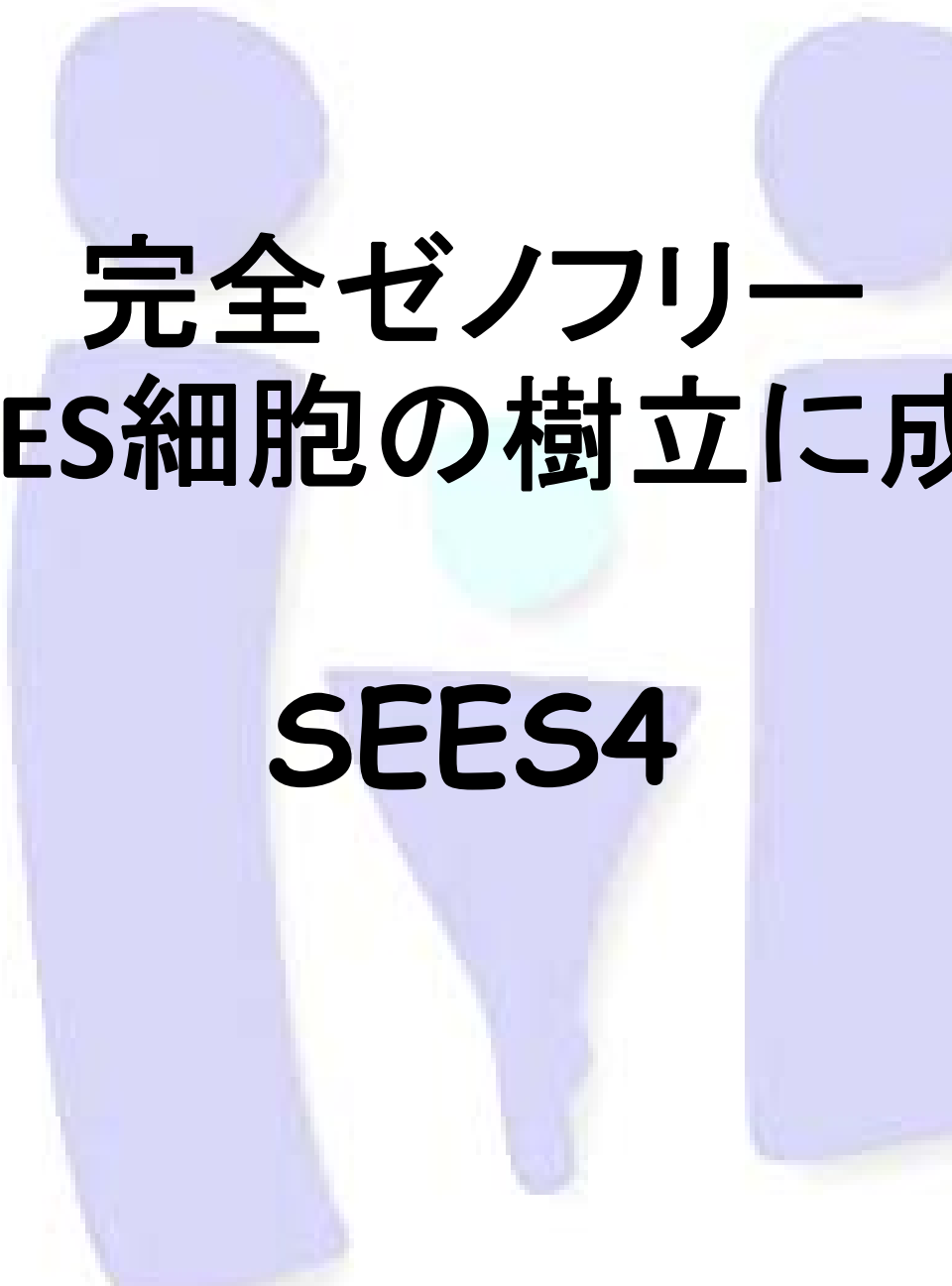


SEES3:46,XY



ヒトES細胞培養系から異種成分を除く

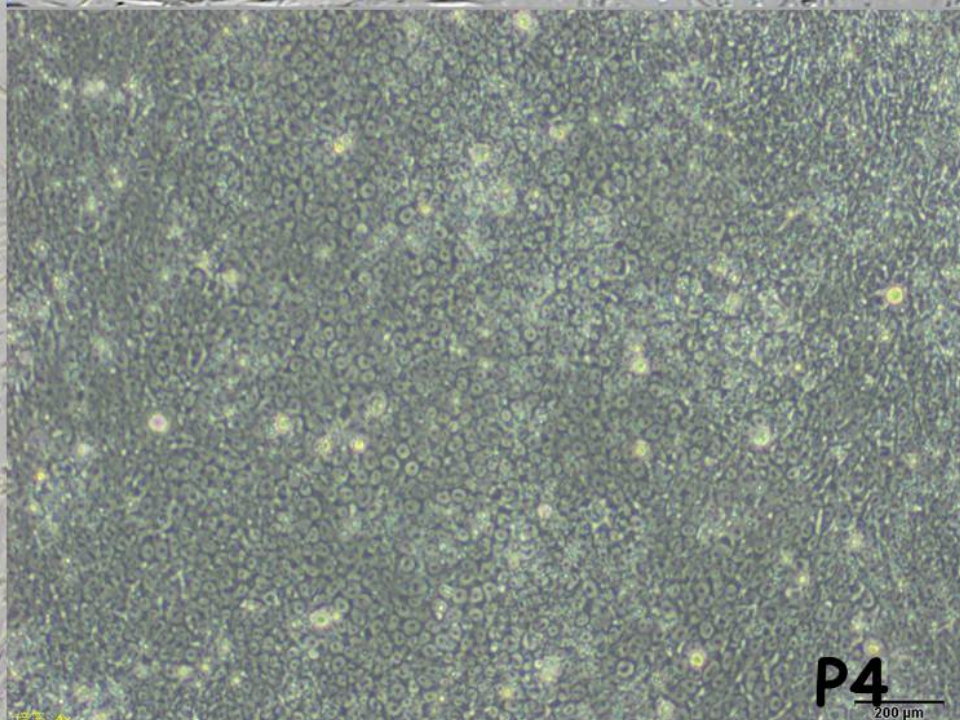
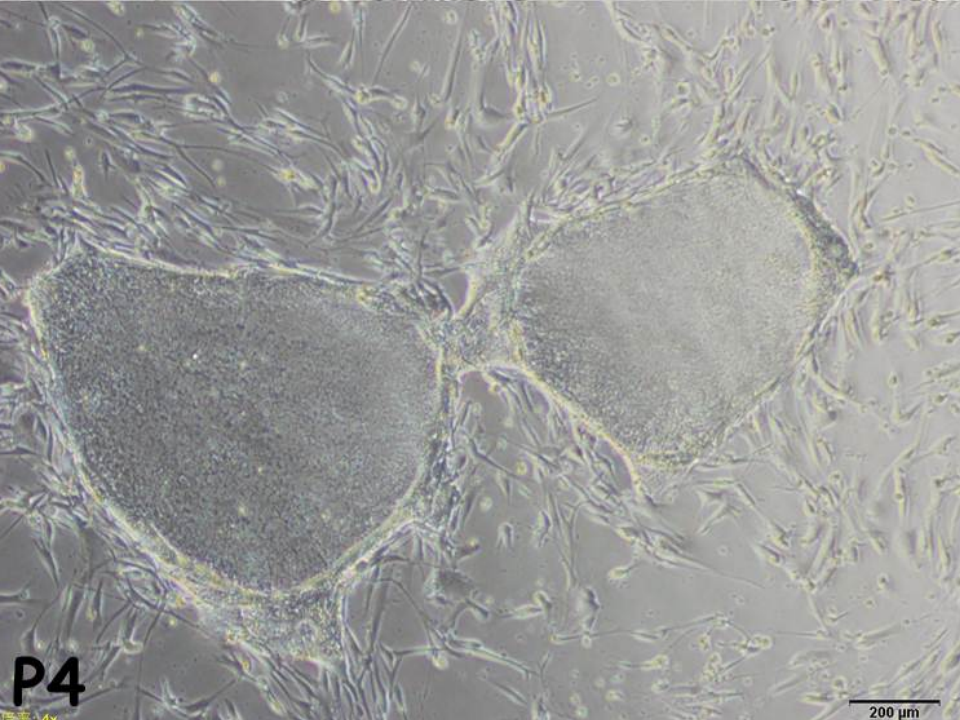
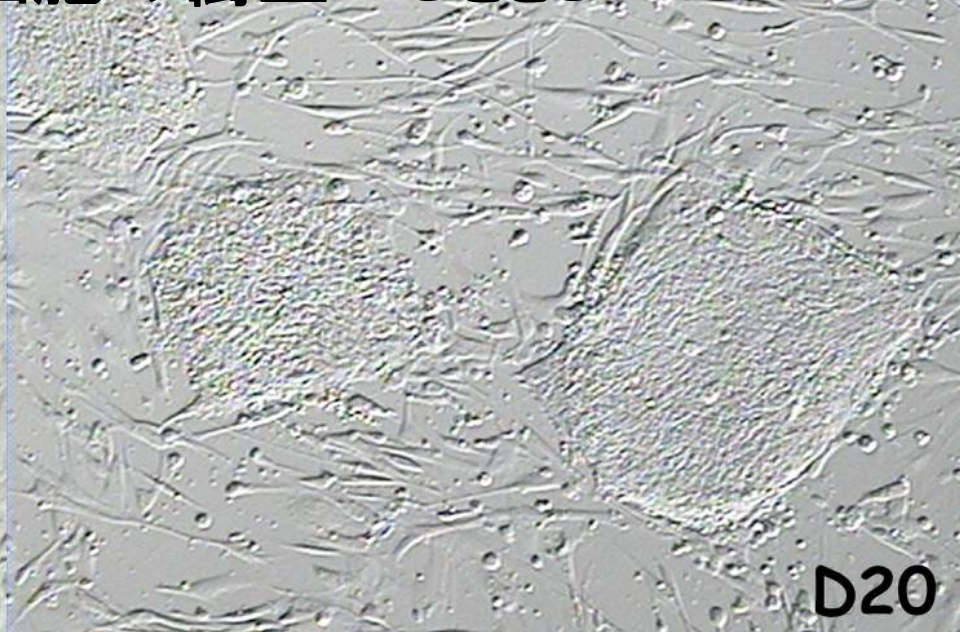


The background features three stylized human figures. Two are purple and one is teal, all with rounded heads and simple bodies. They are positioned behind the main text.

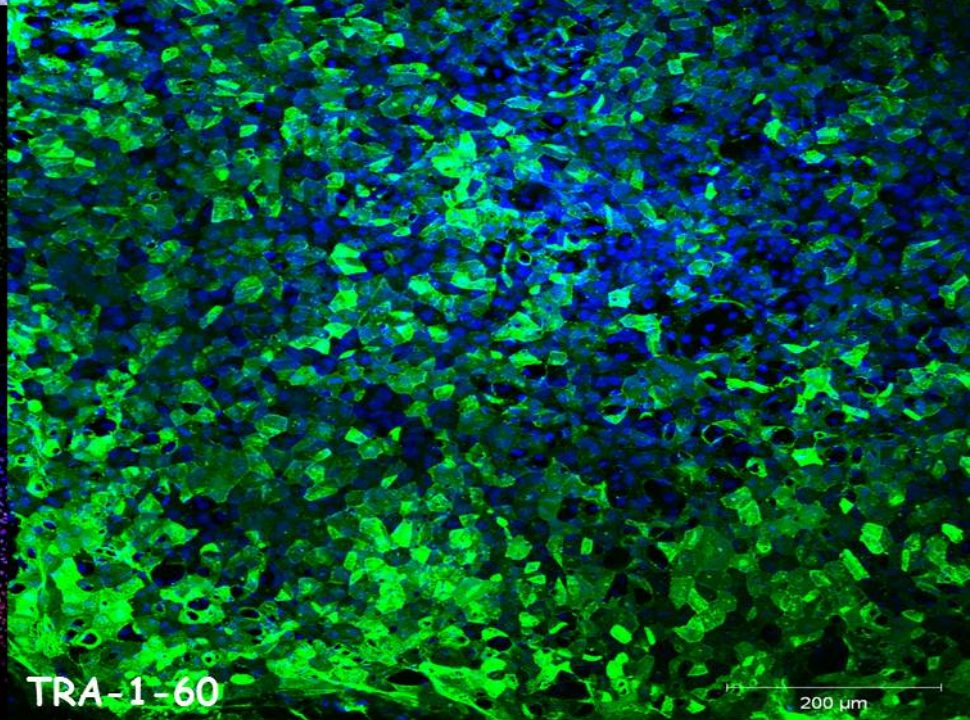
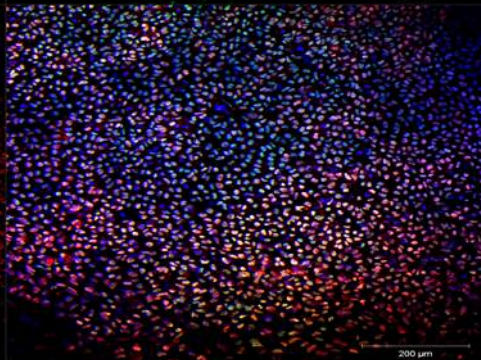
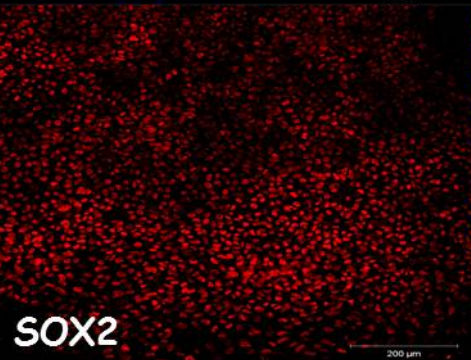
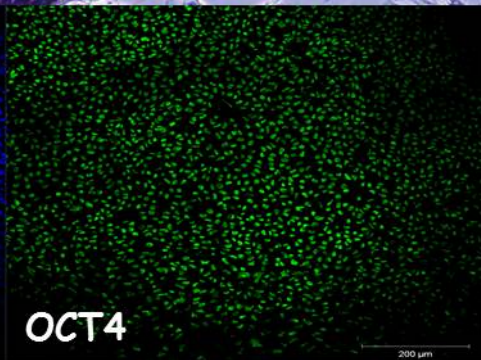
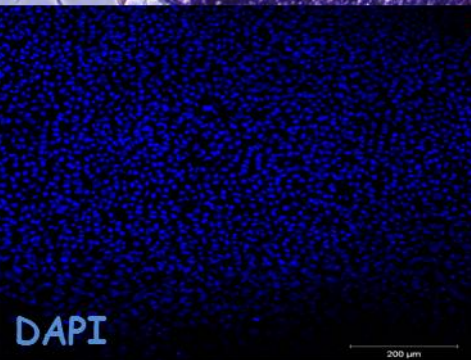
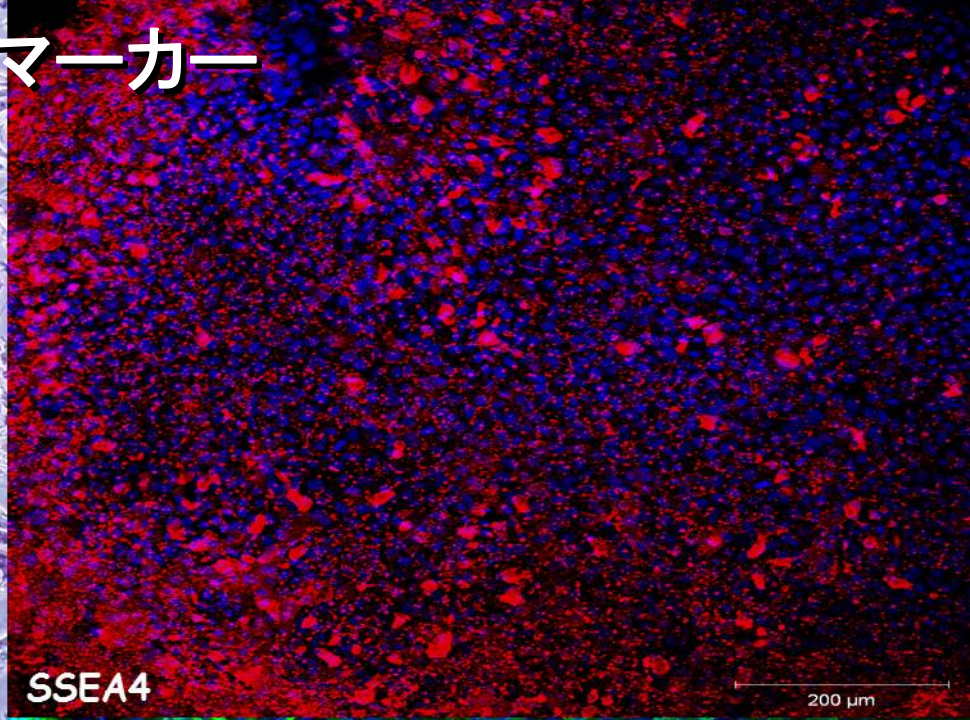
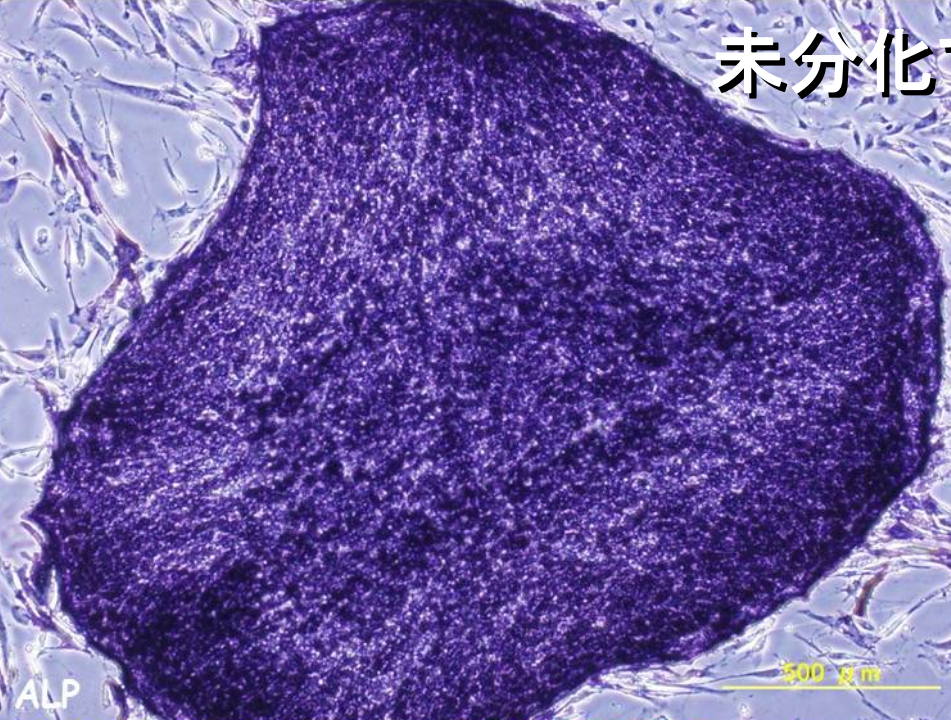
完全ゼノフリー ヒトES細胞の樹立に成功

SEES4

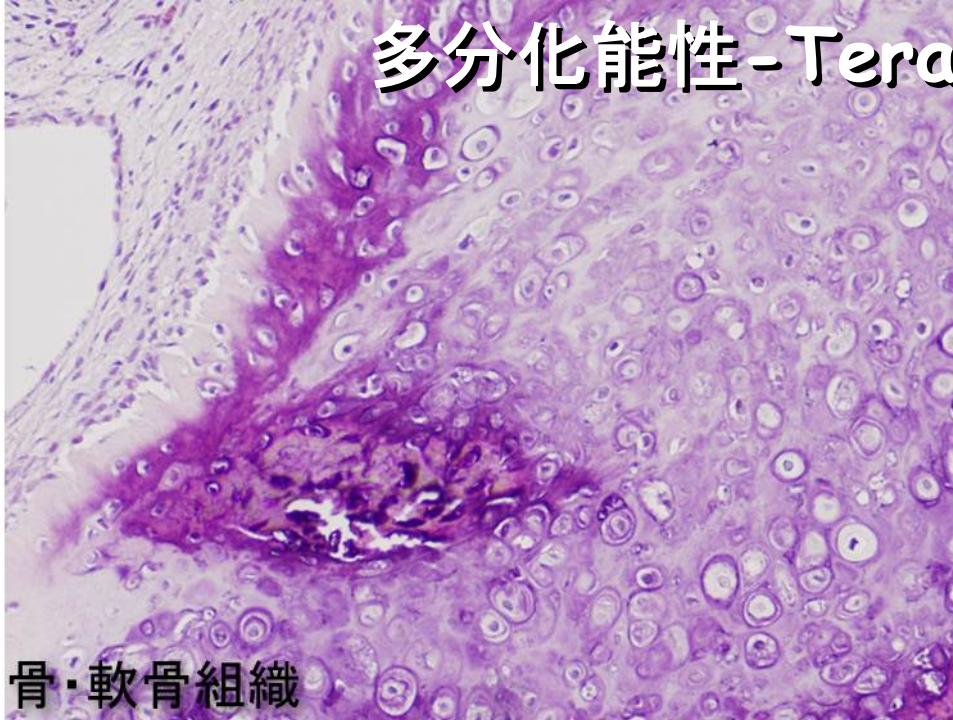
完全ゼノフリーヒトES細胞の樹立～SEES4～



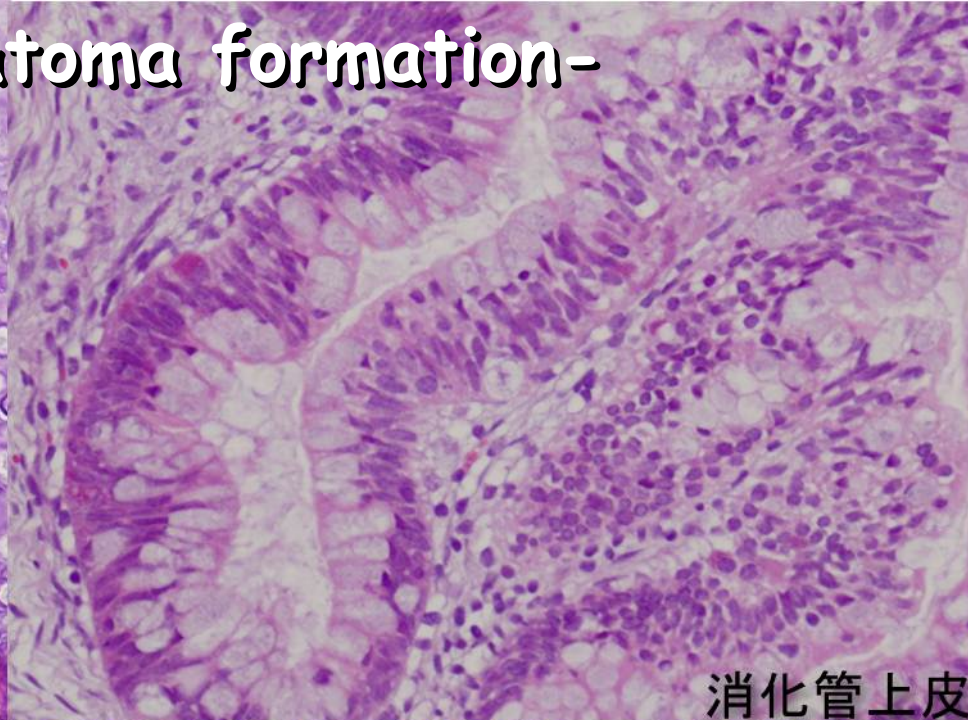
未分化マーカー



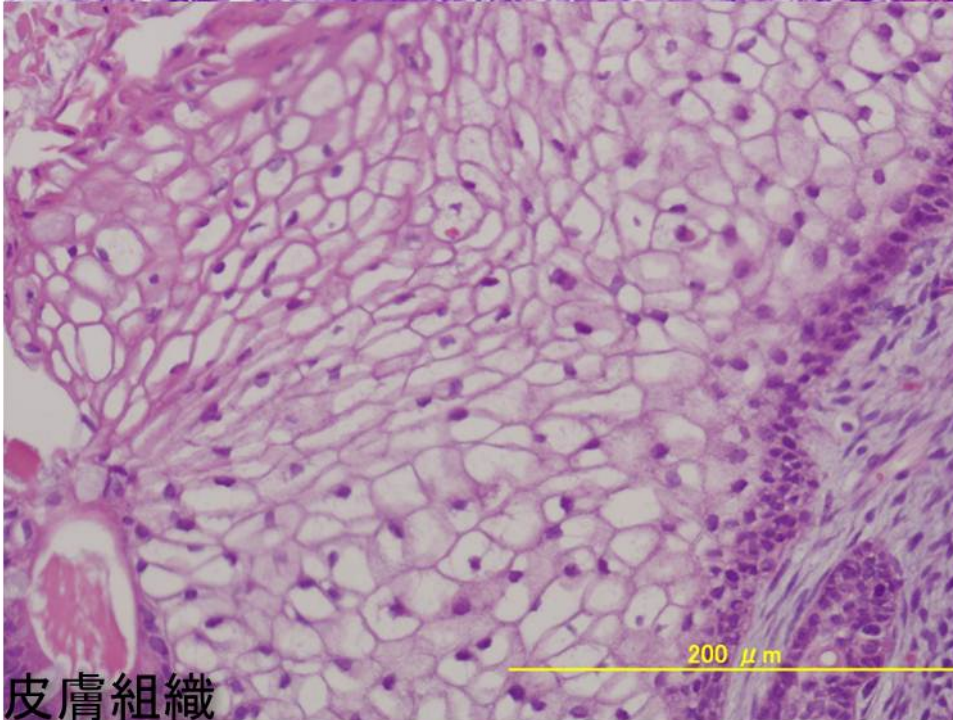
多分化能性-Teratoma formation-



骨·軟骨組織

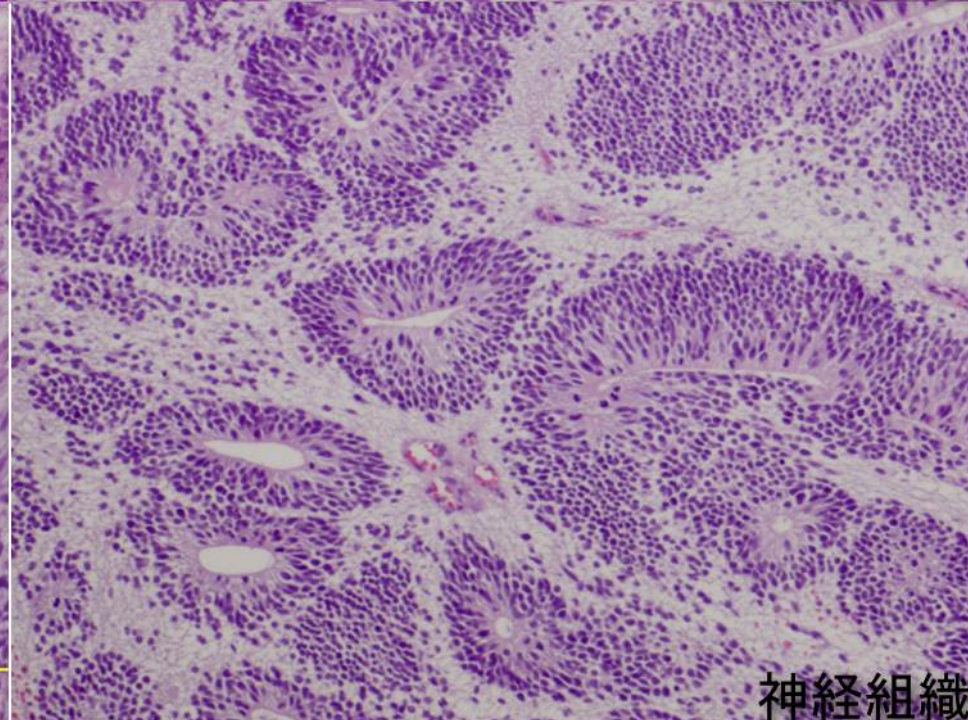


消化管上皮



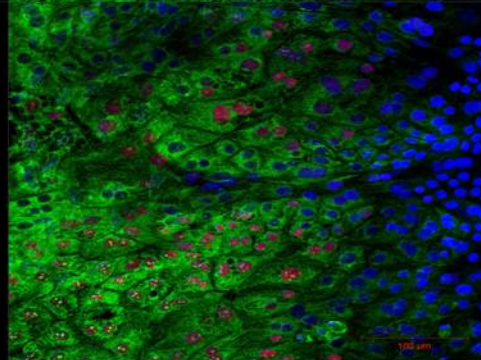
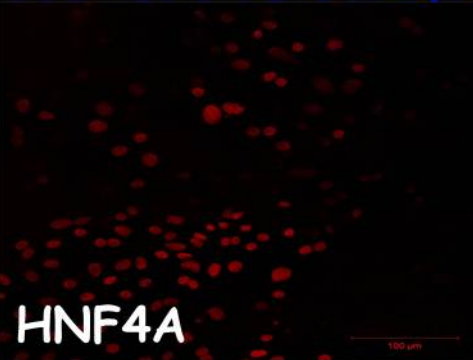
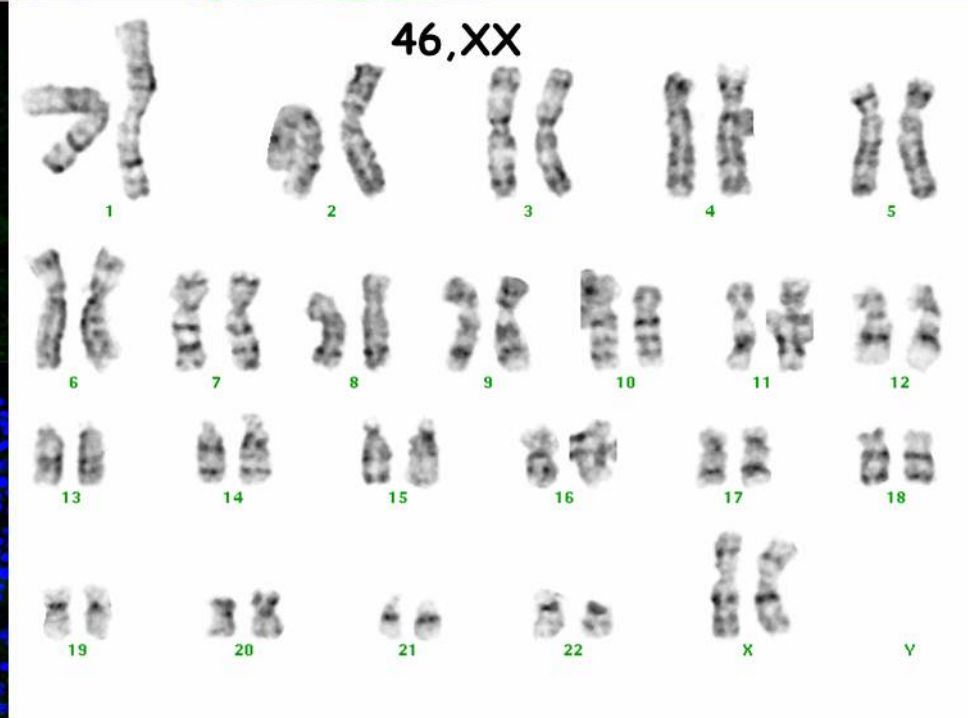
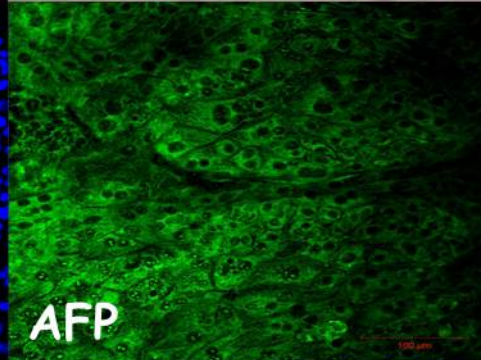
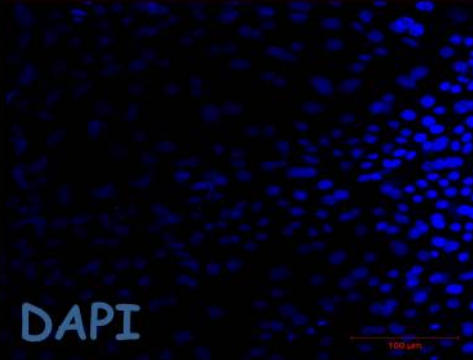
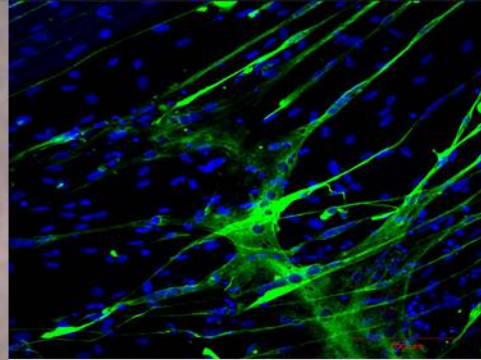
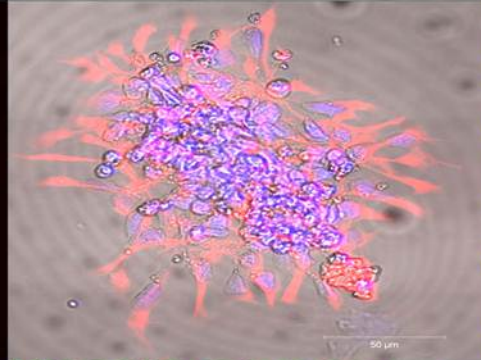
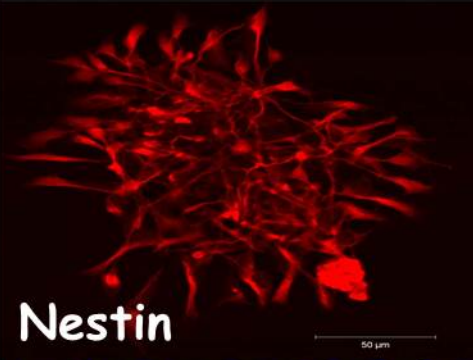
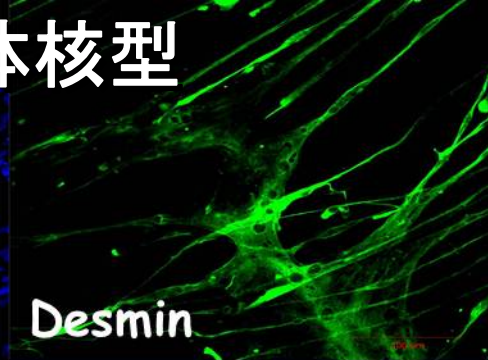
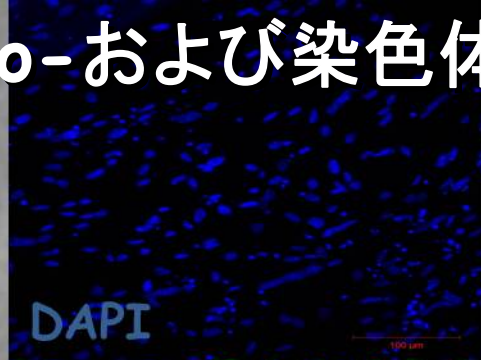
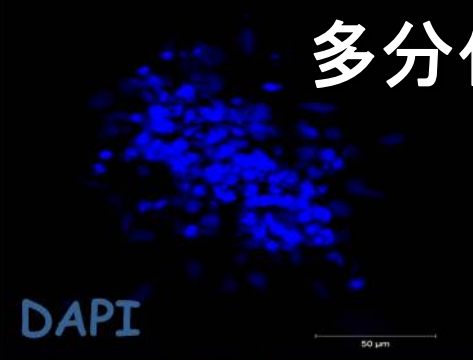
皮膚組織

200 μ m

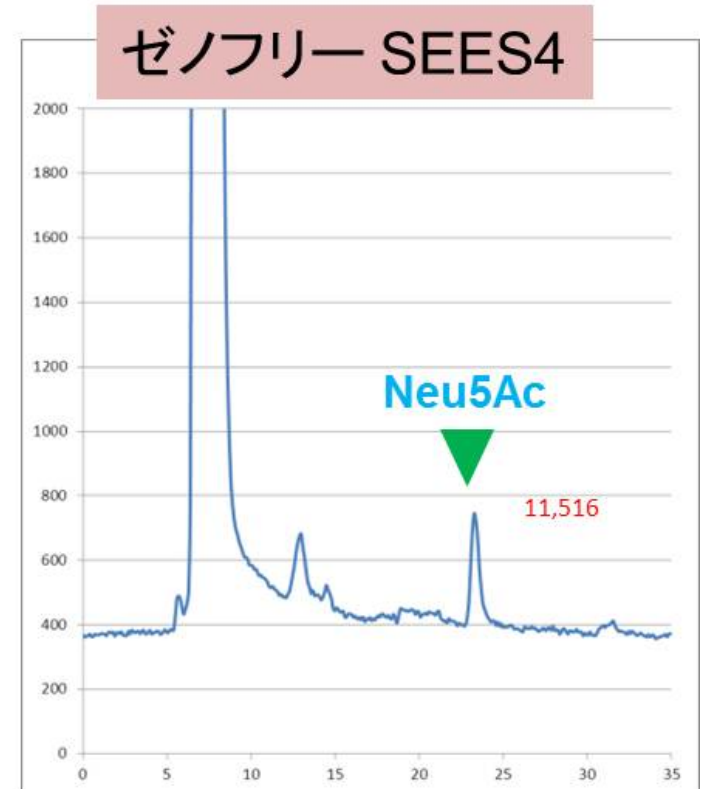
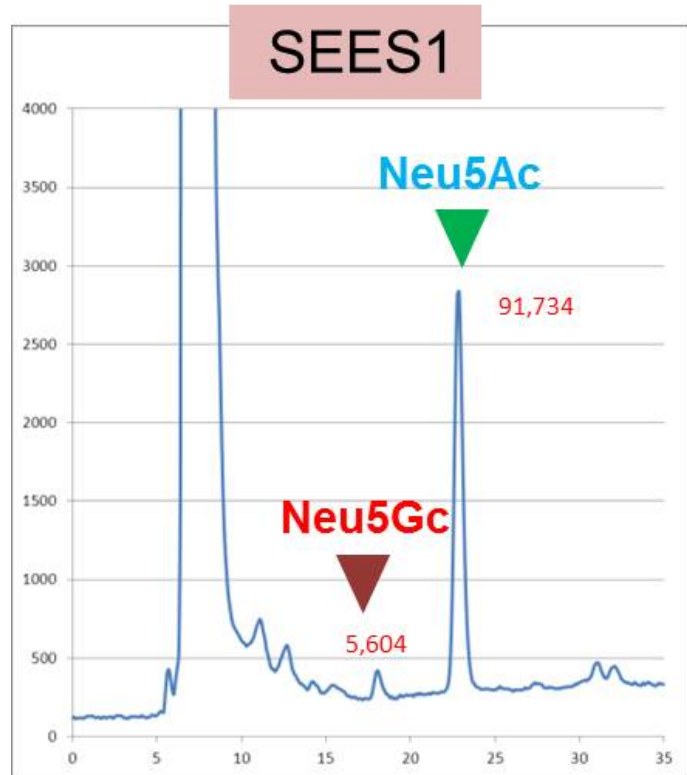


神經組織

多分化能性-in vitro-および染色体核型



ヒトES細胞非ヒト型シアル酸解析



結語

1. ヒトES細胞を用いた臨床応用は進んでいる
・ACT社による臨床試験(米国)
2. ヒトES細胞樹立から維持までの基盤技術は確保されている
3. 次世代臨床応用のヒトES細胞(非ヒト型シアル酸フリー)作製に成功



謝辞

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研究所再生医療センター

文部科学省
「再生医療の実現化プロジェクト」