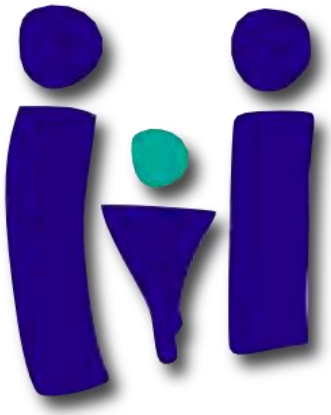
資料1

臨床応用を目指す
ヒトES細胞研究の現状

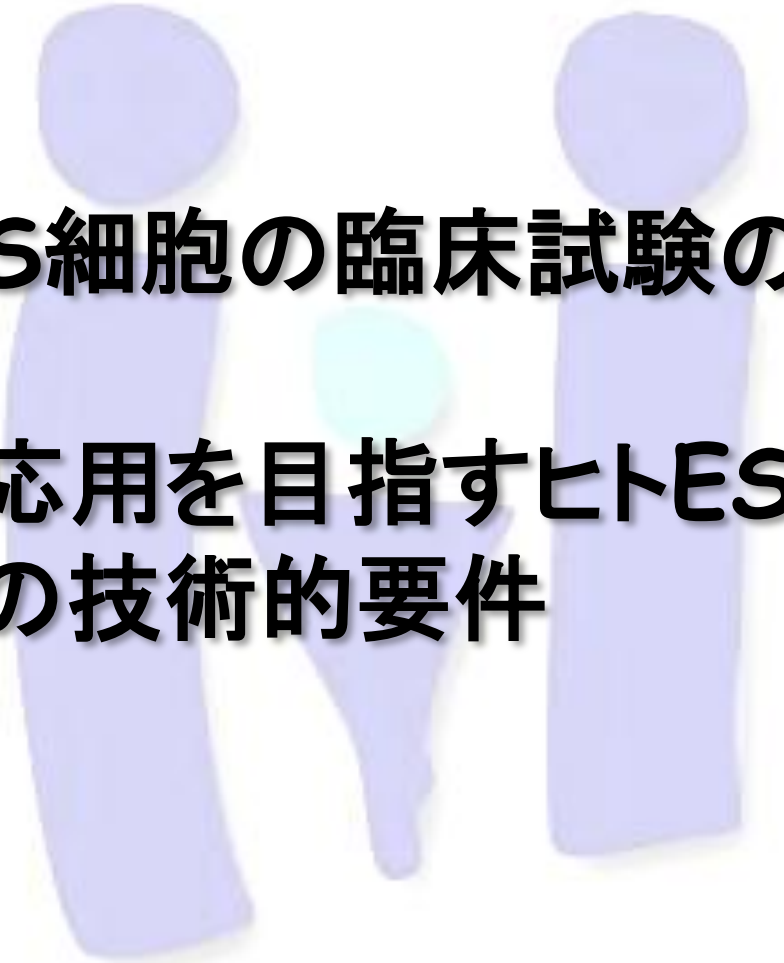
日時：平成24年1月25日
於　：厚生労働省



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、梅澤明弘

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

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

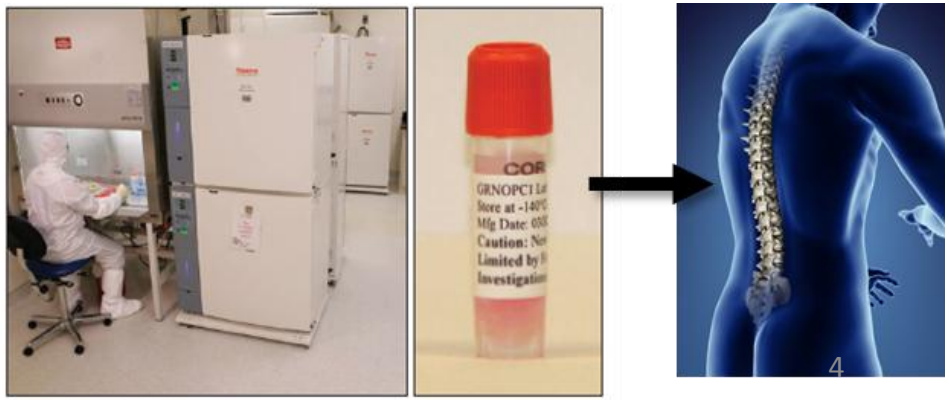
Sponsor:	Geron Corporation
Information provided by (Responsible Party):	Geron Corporation
ClinicalTrials.gov Identifier:	NCT01217008

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).

Condition	Intervention	Phase
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.

(Oct. 20th, 2011)

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; $2x10^6$

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）

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/

ACT社による取り組み

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).

Condition	Intervention	Phase
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)

ACT
Advanced Cell Technology


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)

ACT社による取り組み

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.

Condition	Intervention	Phase
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

ACT
Advanced Cell Technology

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

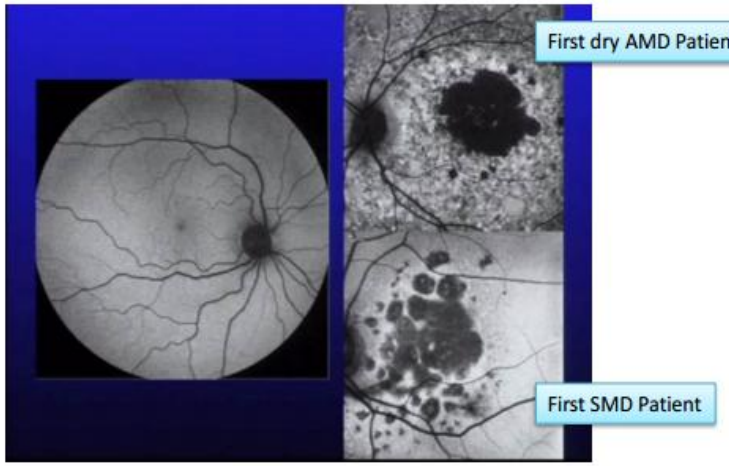
- 12 Patients for each trial, ascending dosages of 50K, 100K, 150K and 200K cells.
  - For each cohort, 1st patient treatment followed by 6 week DMSB review before remainder of cohort.
- Patients are monitored - *including high definition imaging of retina*

Permit comparison of RPE and photoreceptor activity before and after treatment

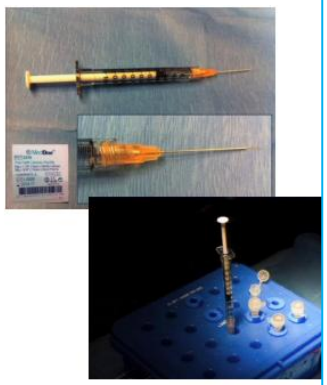
High Definition Spectral Domain Optical Coherence Tomography (SD-OCT)
Retinal Autofluorescence

Engraftment and photoreceptor activity data available early in Phase I study.

ACT社による取り組み



臨床試験患者（2名）の眼底写真



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/

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.*

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

- 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.*

ACT臨床試験がウィルズ・アイ・ホスピタルで承認

Press Releases

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

MARLBOROUGH, Mass. — Jan. 18, 2012 – Advanced Cell Technology, Inc. ("ACT"; OTCBB: ACTC), a leader in the field of regenerative medicine, announced today that the Wills Eye Institute in Philadelphia has received institutional review board (IRB) approval as a site for the Phase 1/2 clinical trial for dry age-related macular degeneration (dry AMD) using human embryonic stem cell (hESC)-derived retinal pigment epithelial (RPE) cells.

（2012年1月18日）

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）

治験
（commercial clinical trial）
薬事法

臨床研究
（non-commercial clinical trial）
先進医療
高度医療

基礎研究

前臨床
試験

前・非臨床
研究

薬事戦略相談

・1314号
・自己指針
・同種指針
・各種幹細胞指針案

治験

First-in
-Human
Trial

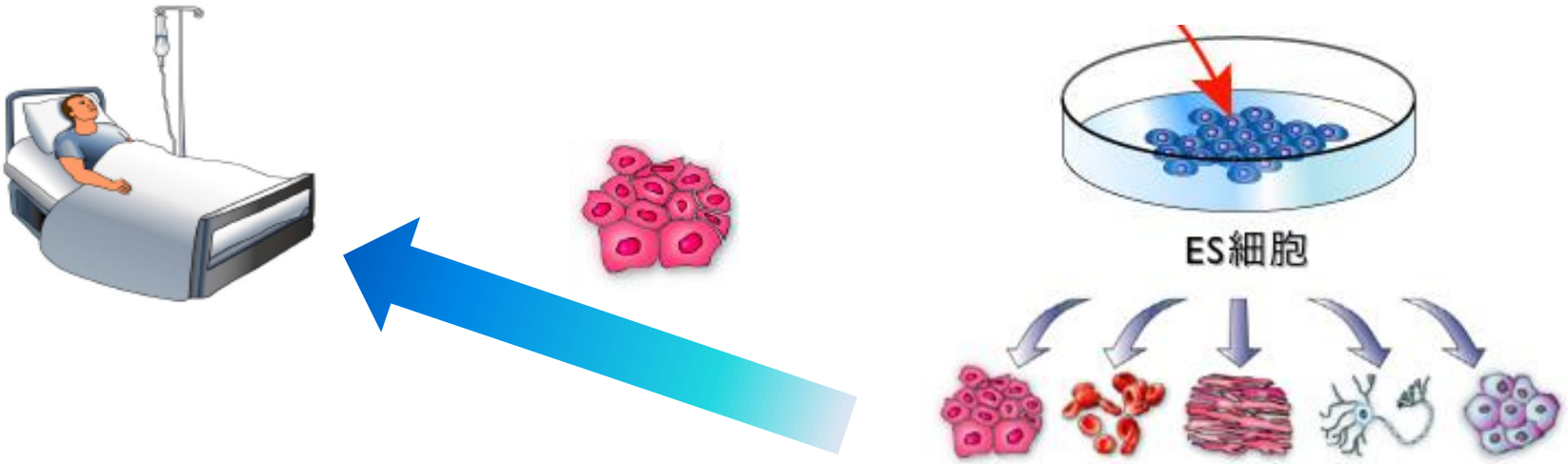
臨床研究

ヒト幹細胞臨床研究
指針

企業による開発、
承認申請
製造販売
臨床利用

先進医療
高度医療

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

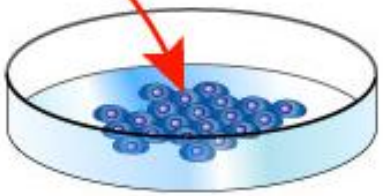
桑実胚

胚盤胞

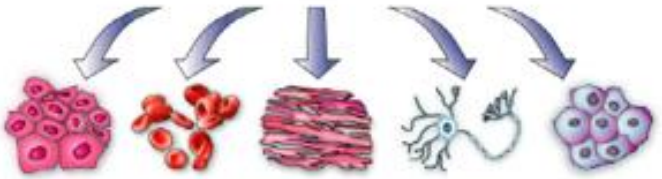
内細胞塊

文部科学省

倫理



ES細胞



厚生労働省

倫理

安全

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

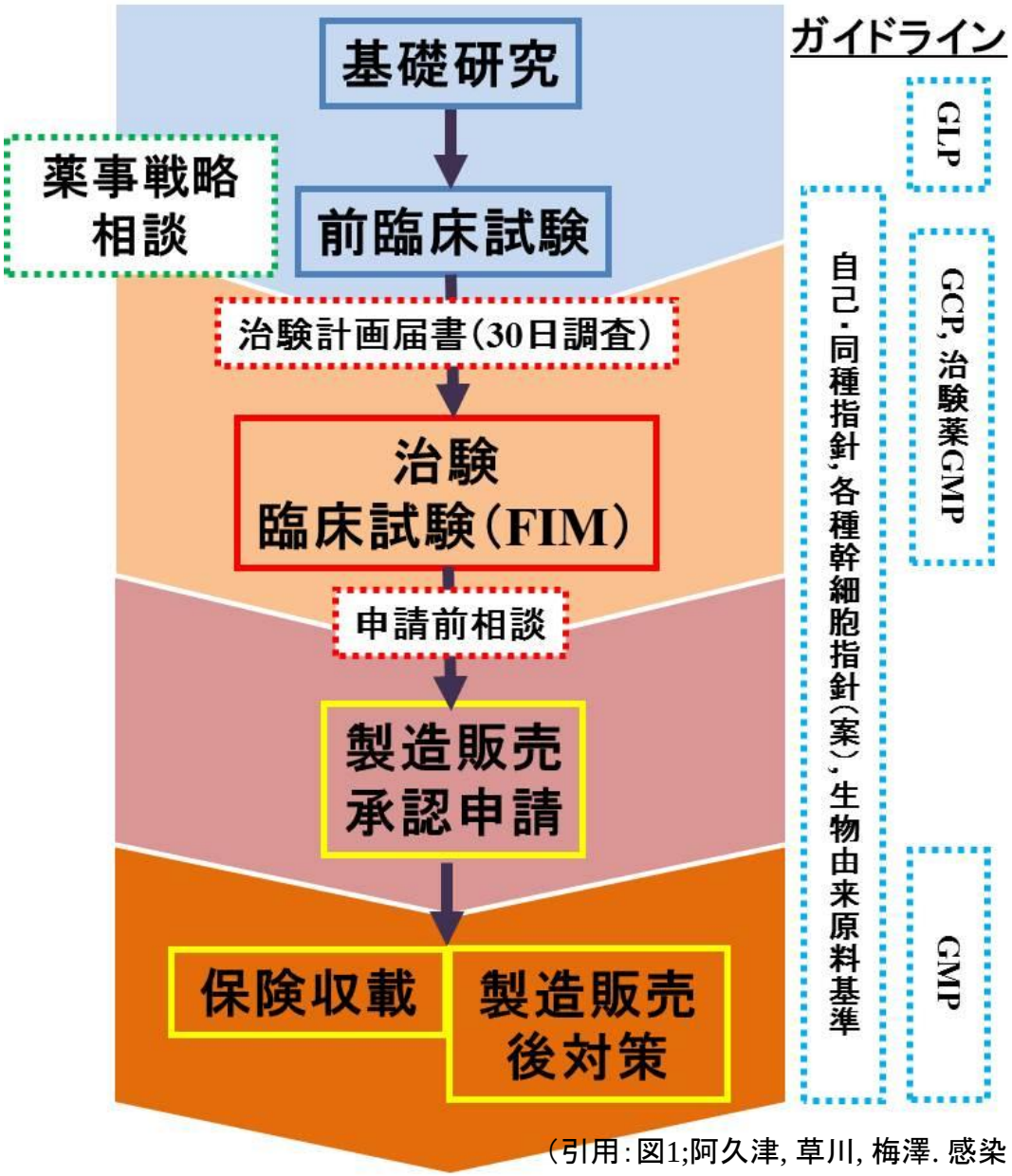
医師法

・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）



（引用：図1;阿久津, 草川, 梅澤. 感染・炎症・免疫；2012, 41; 324-328）

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

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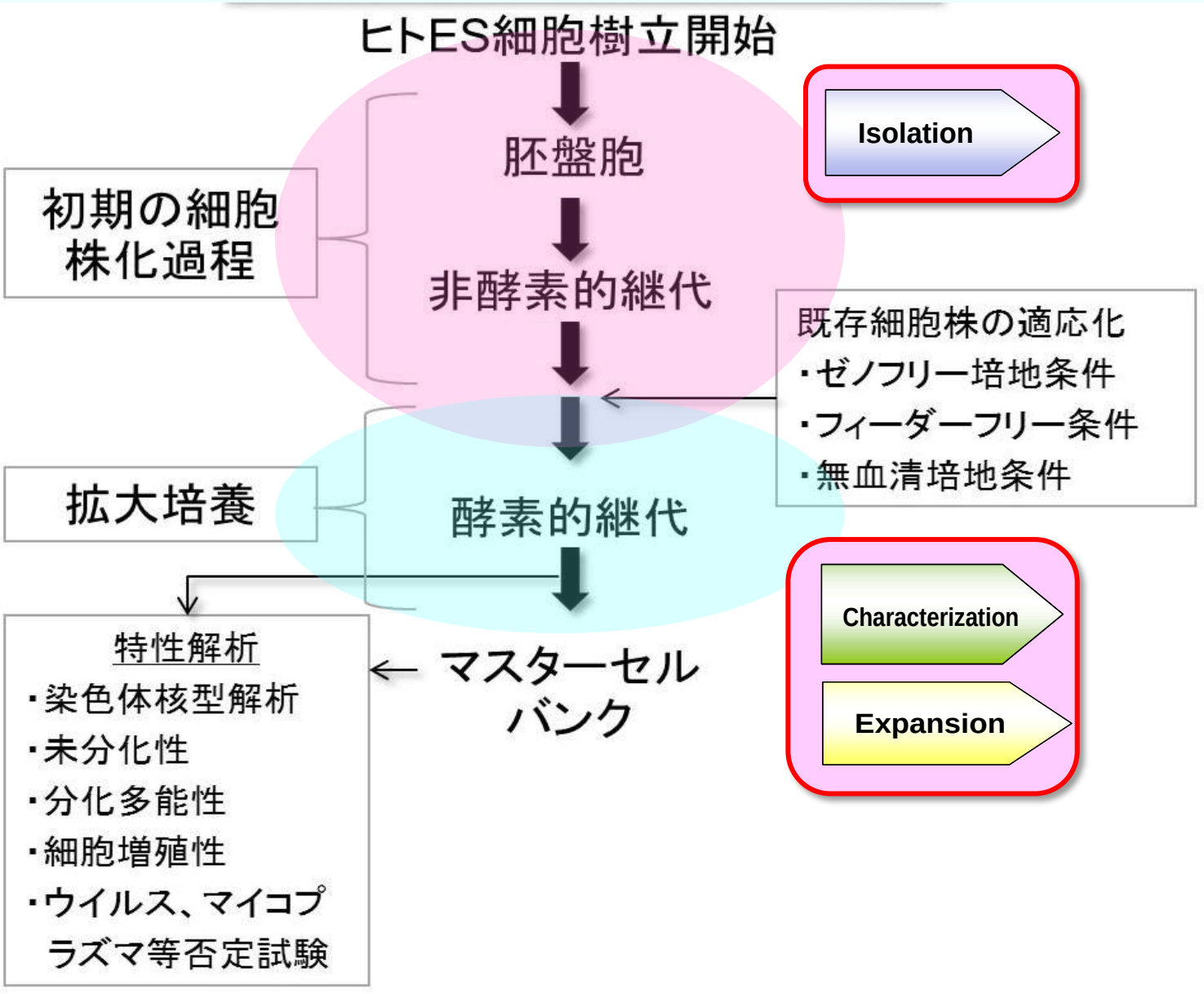
ヒトES細胞による臨床試験の要件

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



（引用：改変図2;阿久津, 草川, 梅澤. 感染・炎症・免疫；2012, 41; 324-328）

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

ヒト多能性細胞の医療応用に必要な技術的要件

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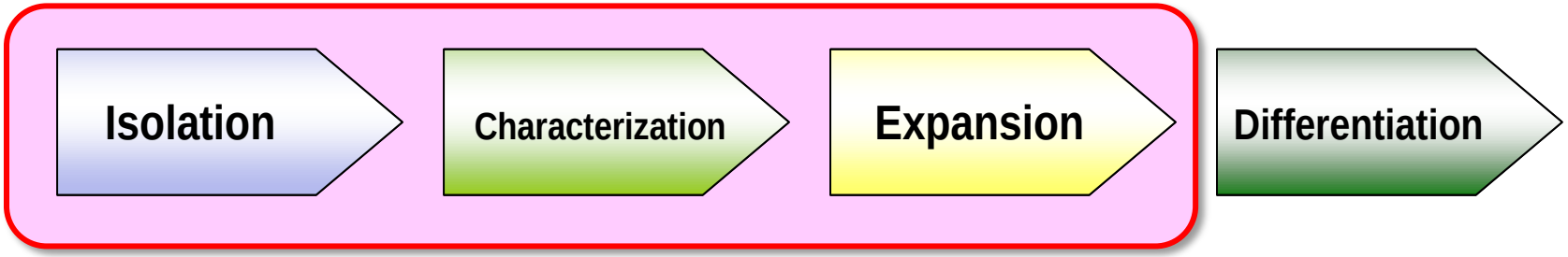


国立成育医療研究センター
ヒトES細胞の樹立

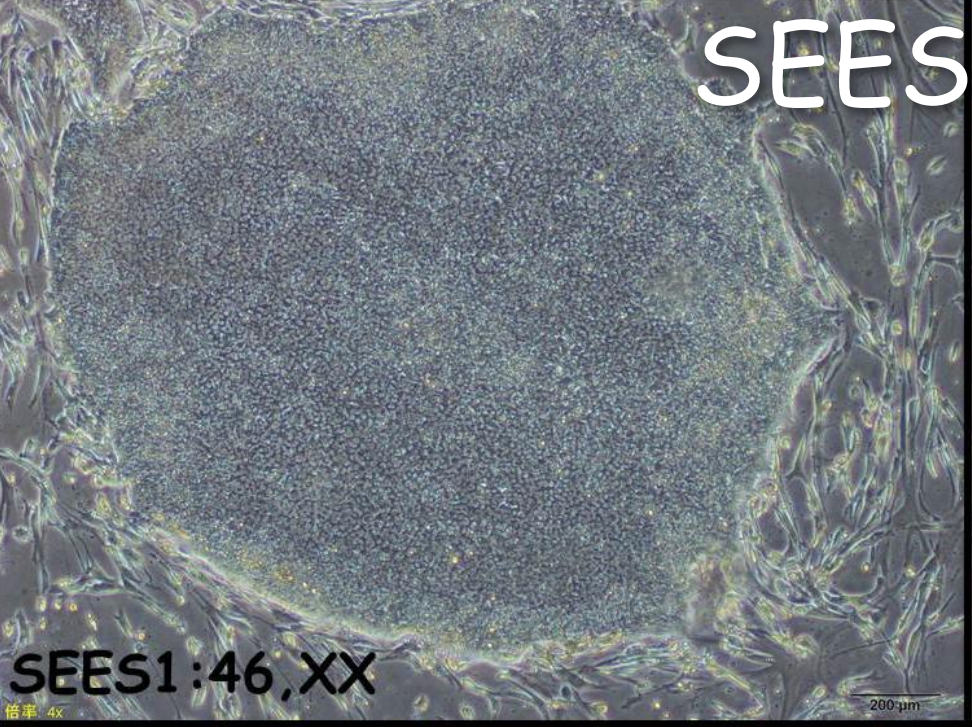
3つのヒトES細胞株樹立

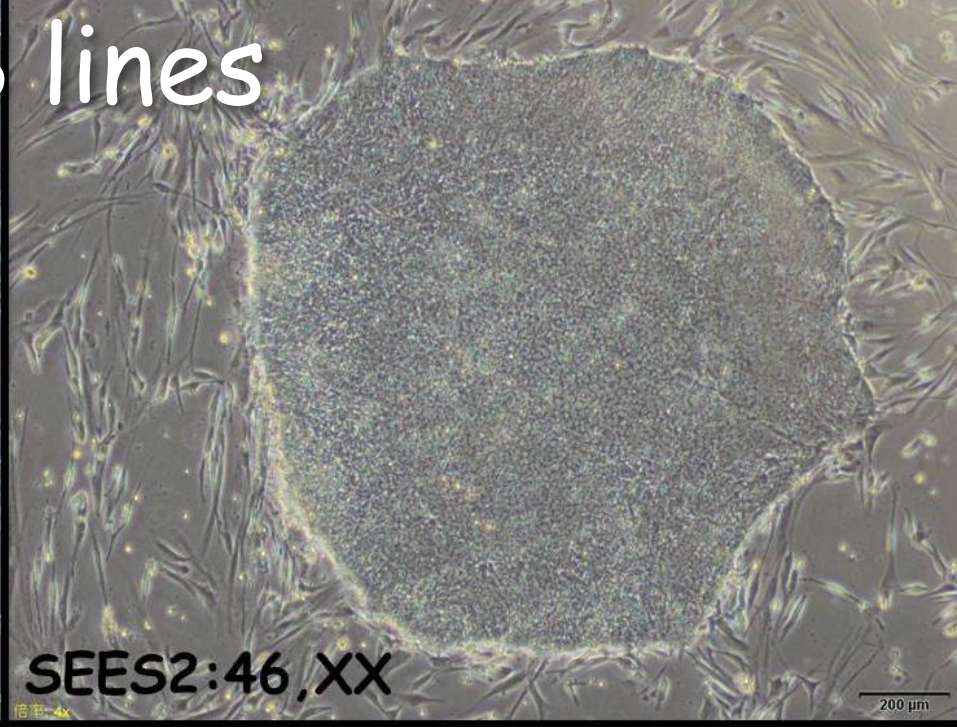
SEiiES

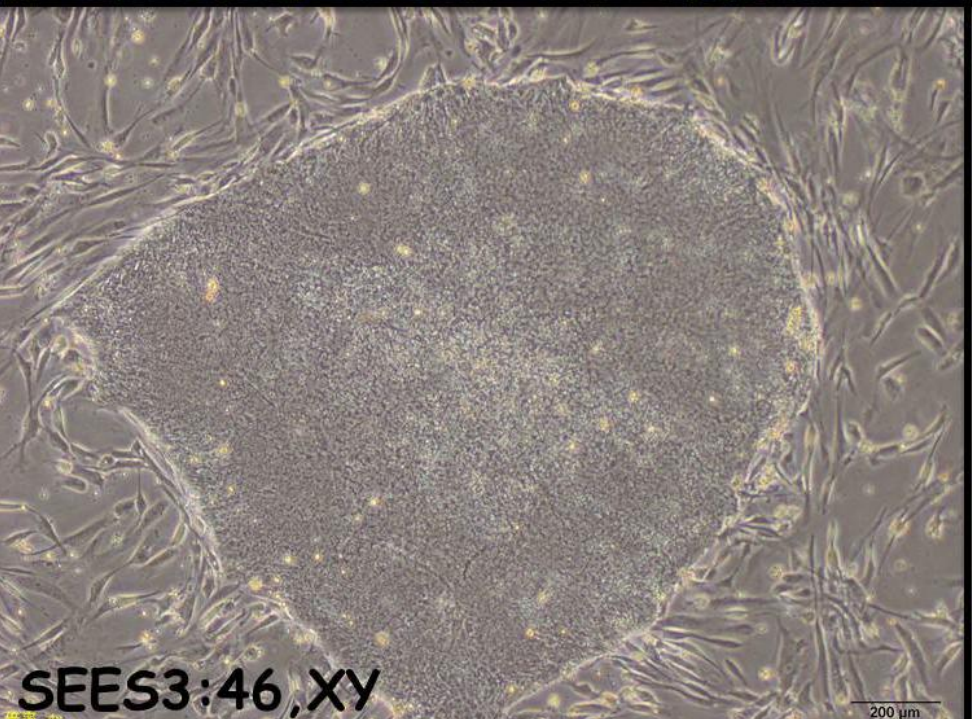
SEES1
SEES2
SEES3

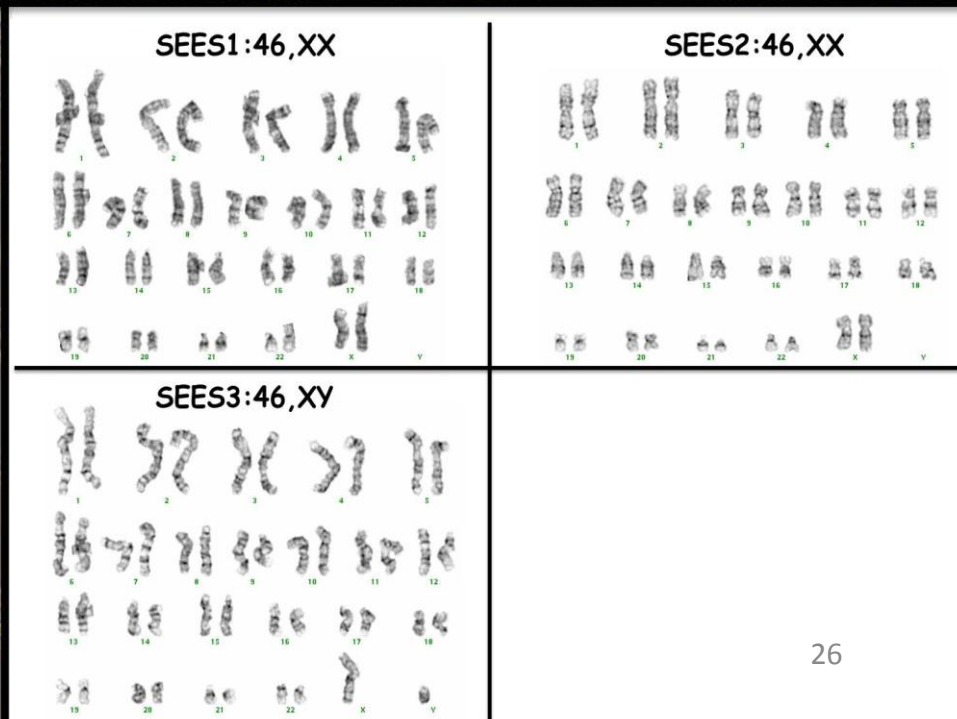
500 μm

SEES lines

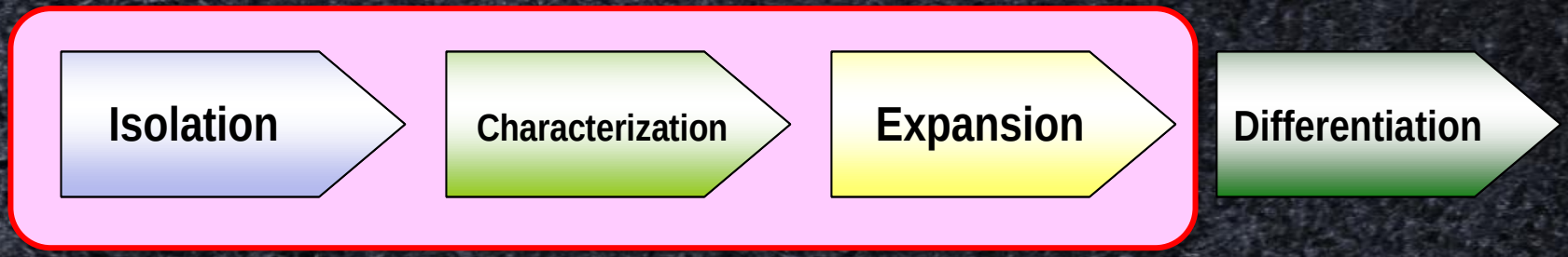

SEES1:46,XX
200 µm


SEES2:46,XX
200 µm


SEES3:46,XY
200 µm


SEES1:46,XX
SEES2:46,XX
SEES3:46,XY

SEES1-3

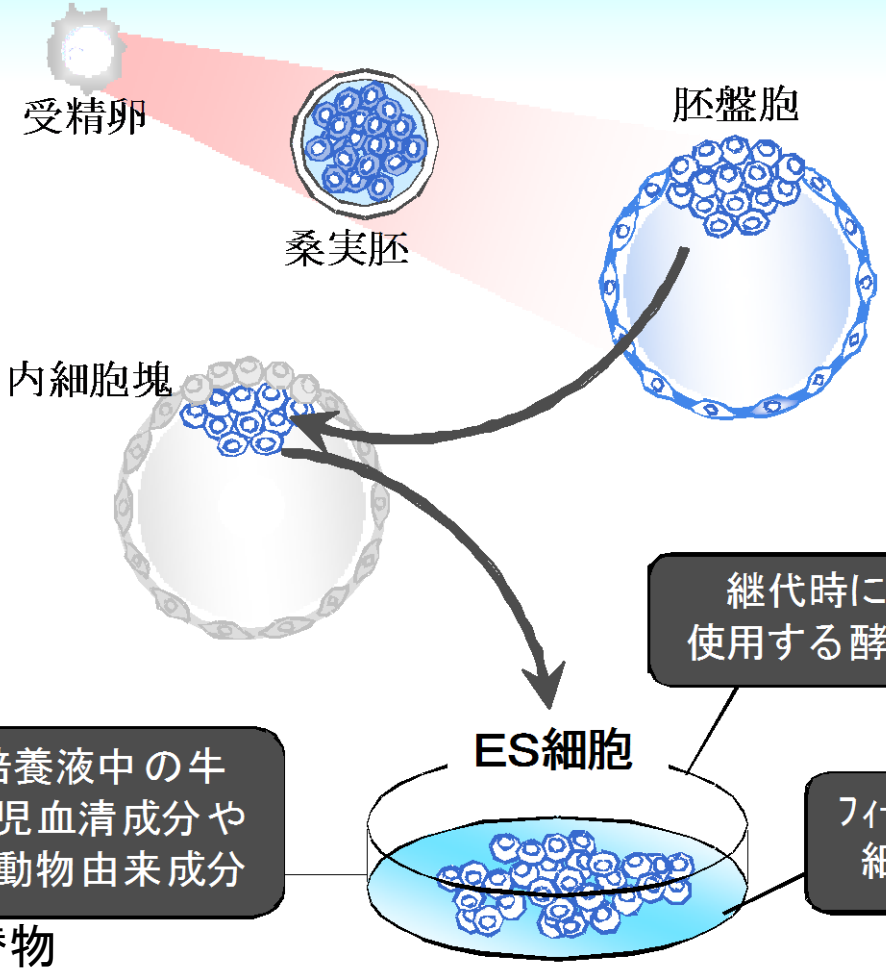


・ヒトES細胞生物学的性質
・染色体核型（正常）

・全て陰性
　無菌試験（一般細菌・真菌検査）
　マイコプラズマ否定試験
　ウイルス否定試験

・エンドトキシン定量（基準値以下）

ヒトES細胞培養系から異種成分を除く



継代時に使用する酵素

- Collagenase Type IV
- Trypsin
  （ウシ、ブタ）

フィーダー細胞

- MEF（マウス）
- STO（マウス）

マトリックス

- ゼラチン（ブタ）
- マトリゲル
  （マウス）

培養液

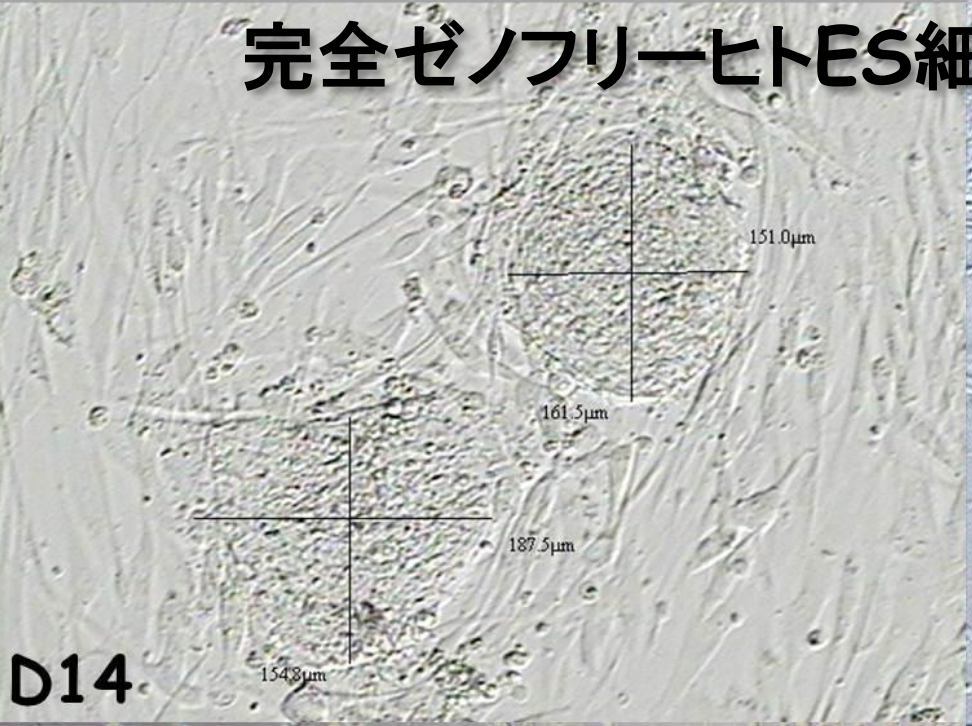
- 牛胎児血清代替物
  (Serum Replacement)
- 牛アルブミン
- 牛脳組織抽出物
  等

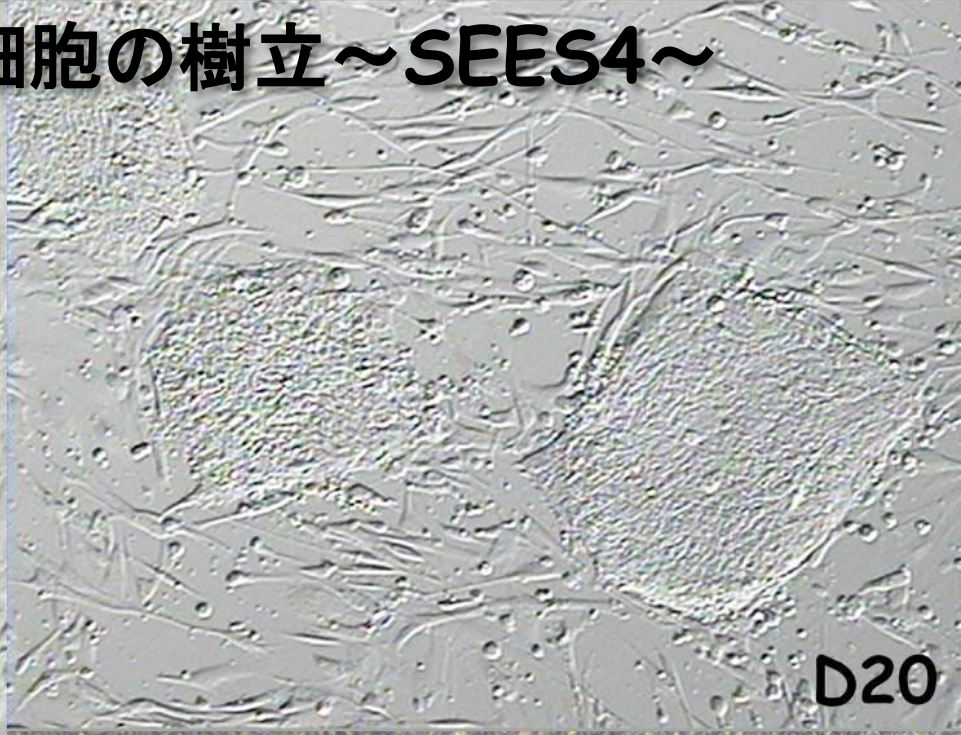
※ ■ ：動物由来成分使用箇所

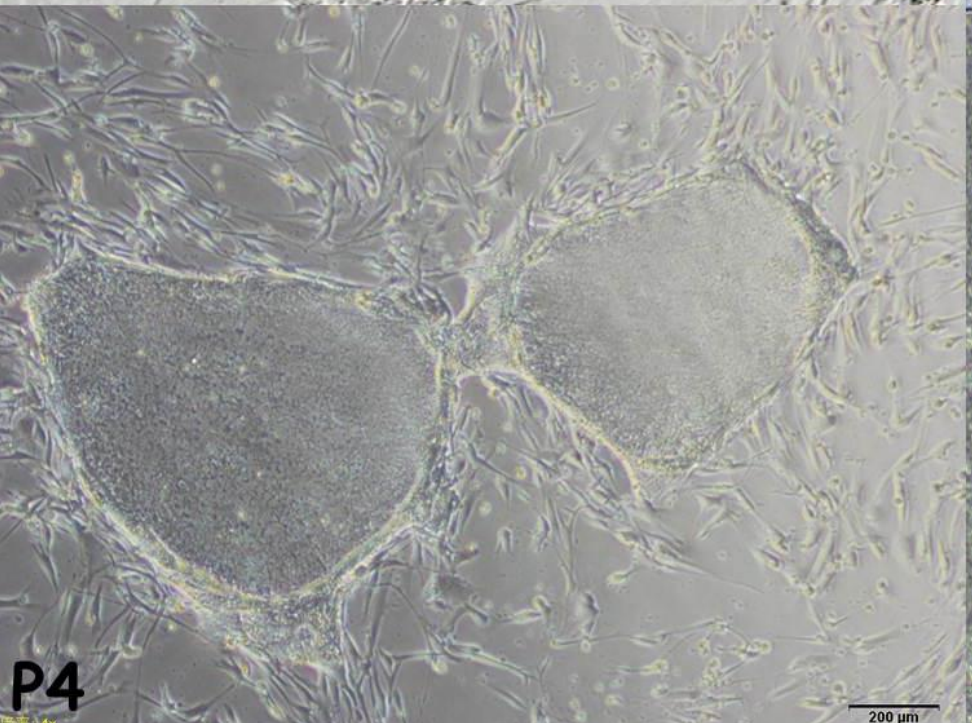
完全ゼノフリー
ヒトES細胞の樹立に成功

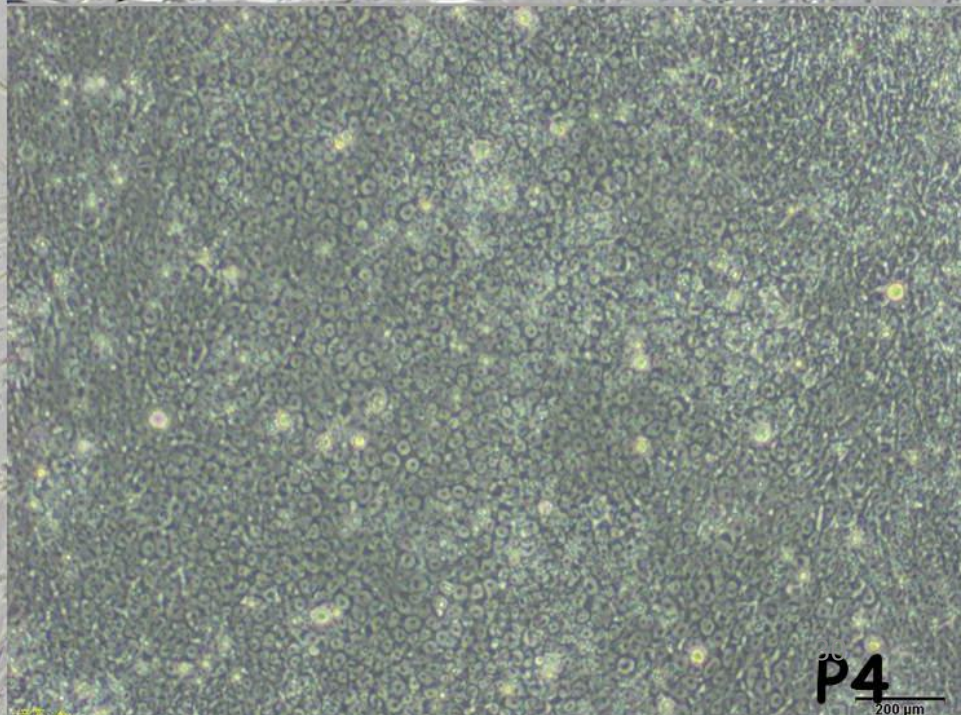
SEES4

完全ゼノフリーヒトES細胞の樹立～SEES4～

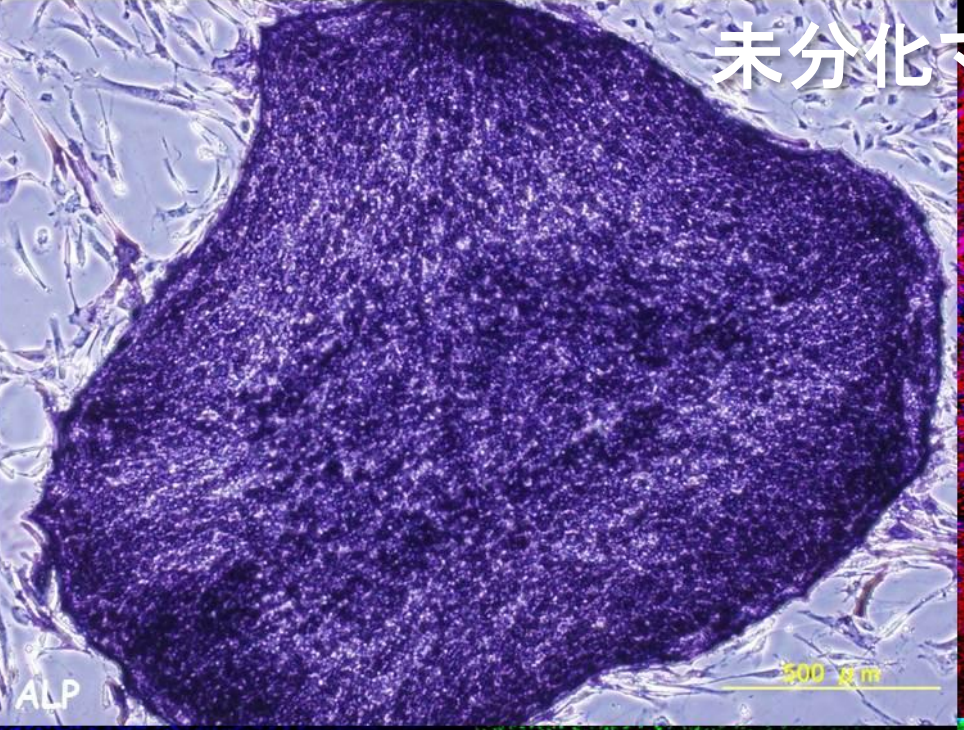


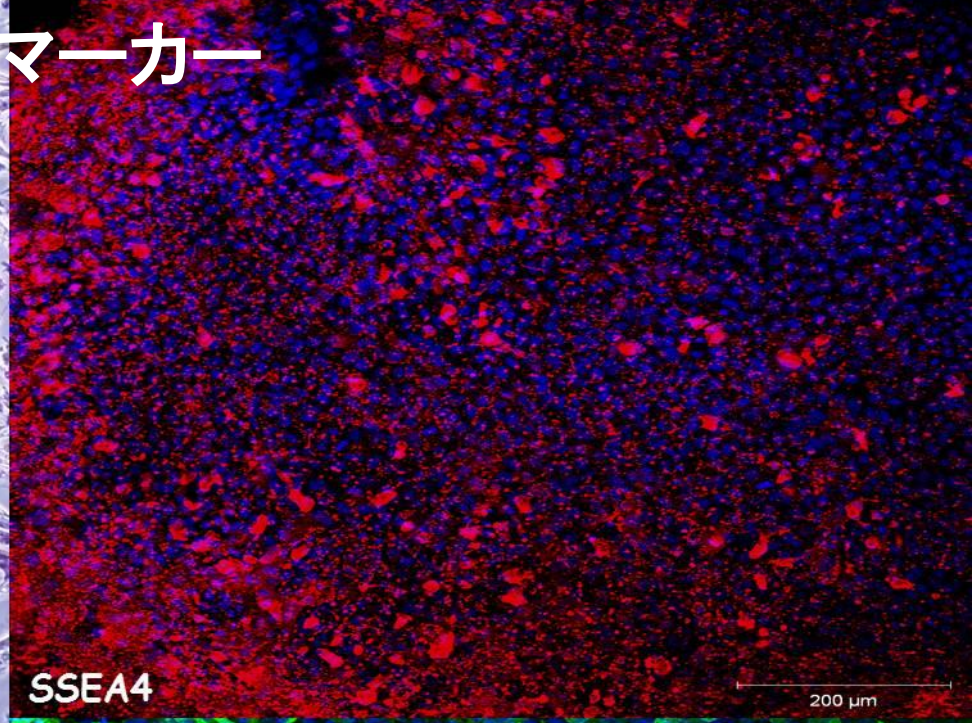


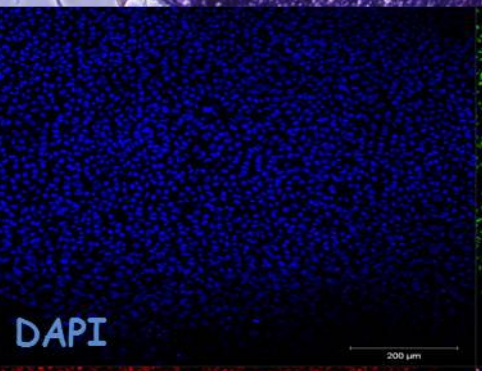


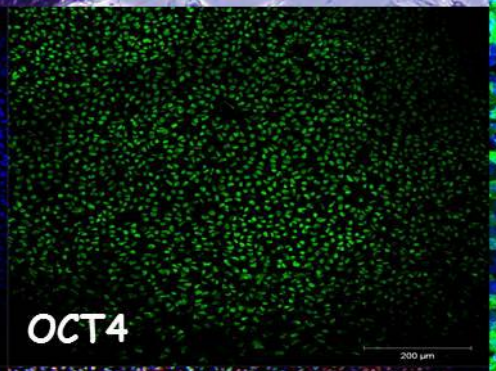


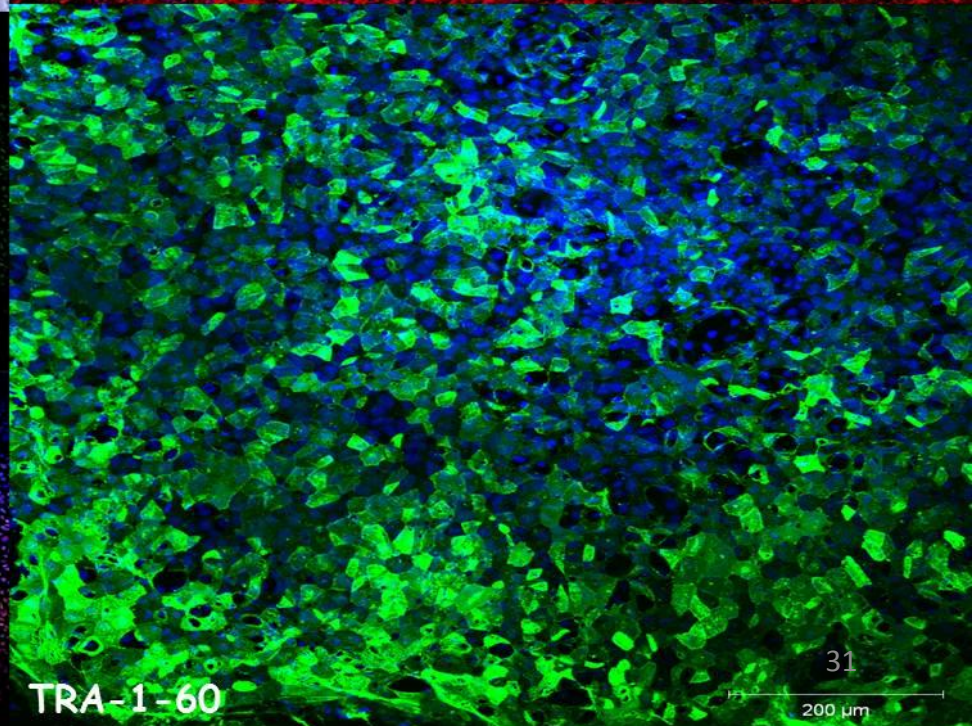
未分化マーカー

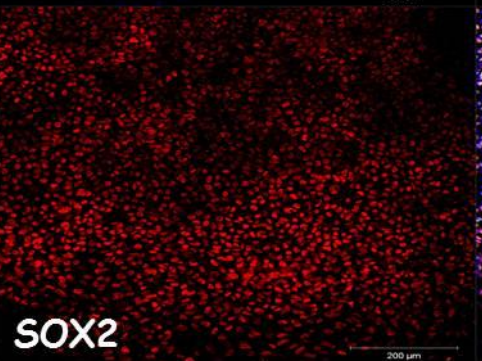

ALP
500 µm

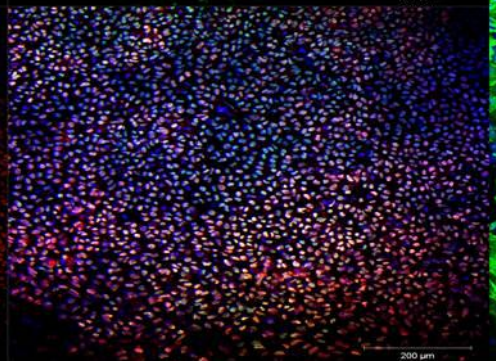

SSEA4
200 µm


DAPI
200 µm

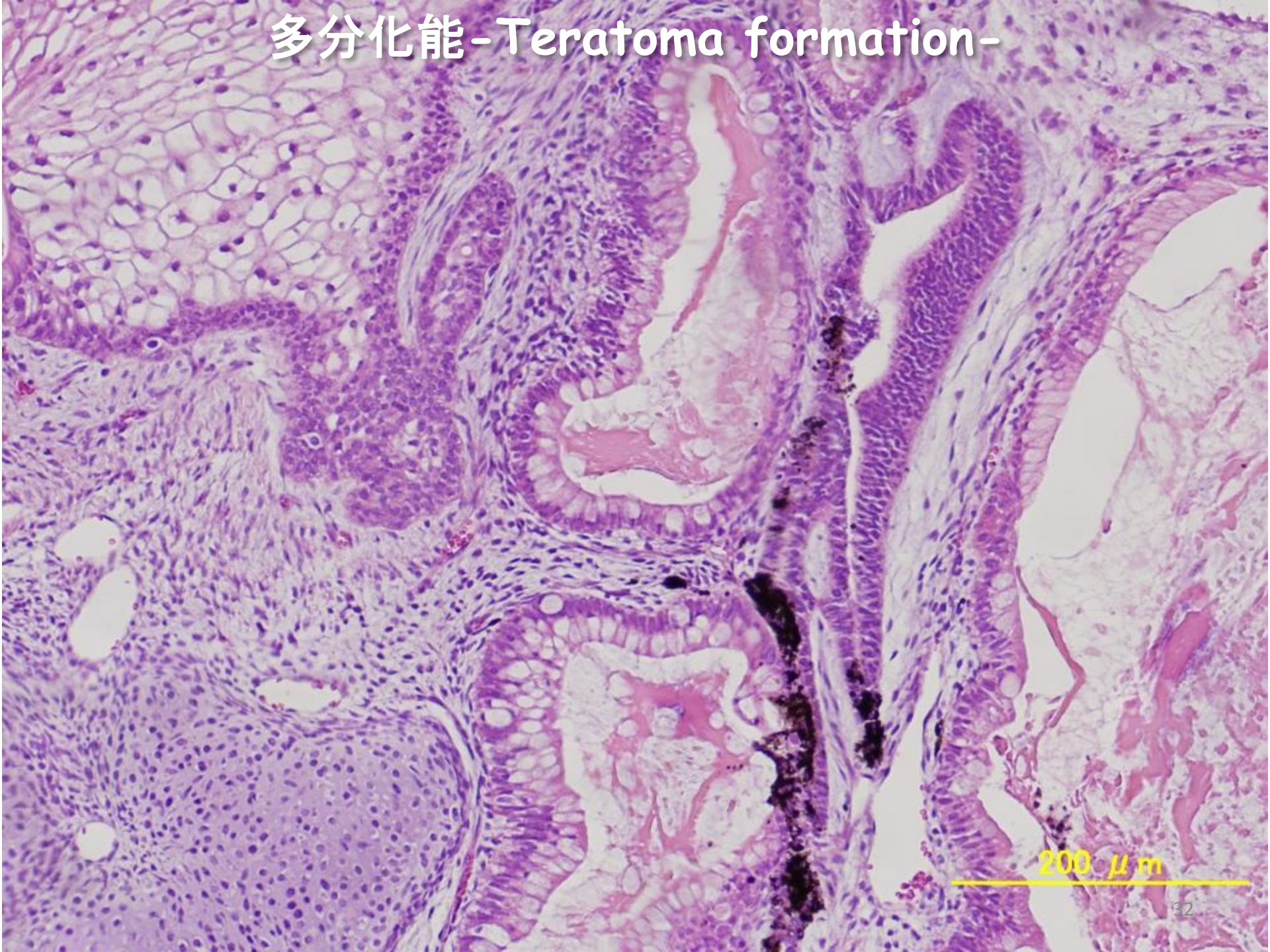

OCT4
200 µm


TRA-1-60
200 µm

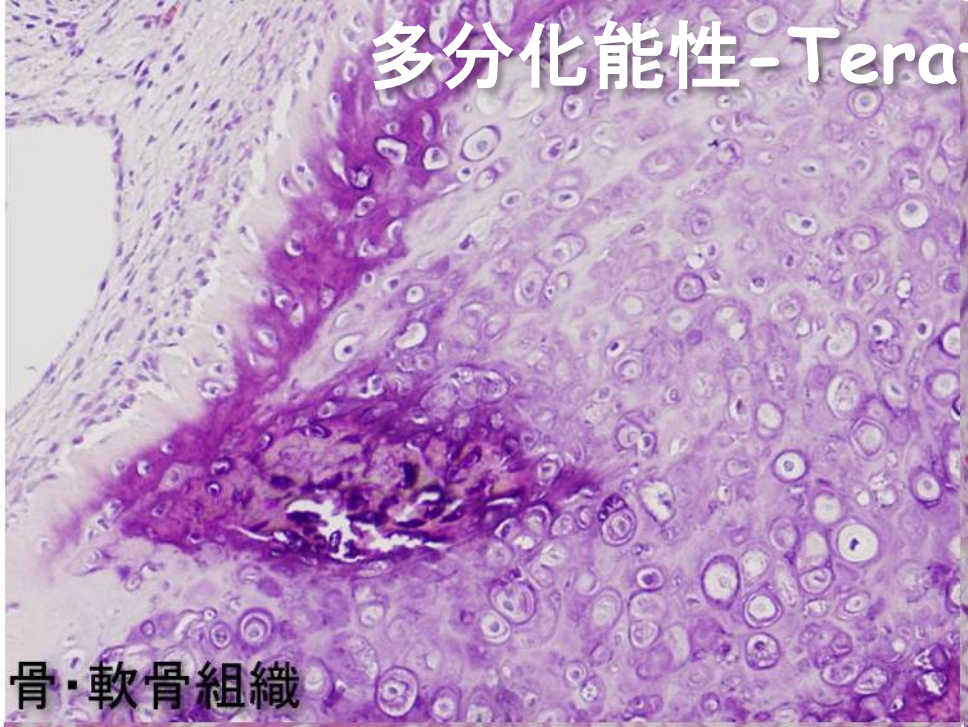

SOX2
200 µm

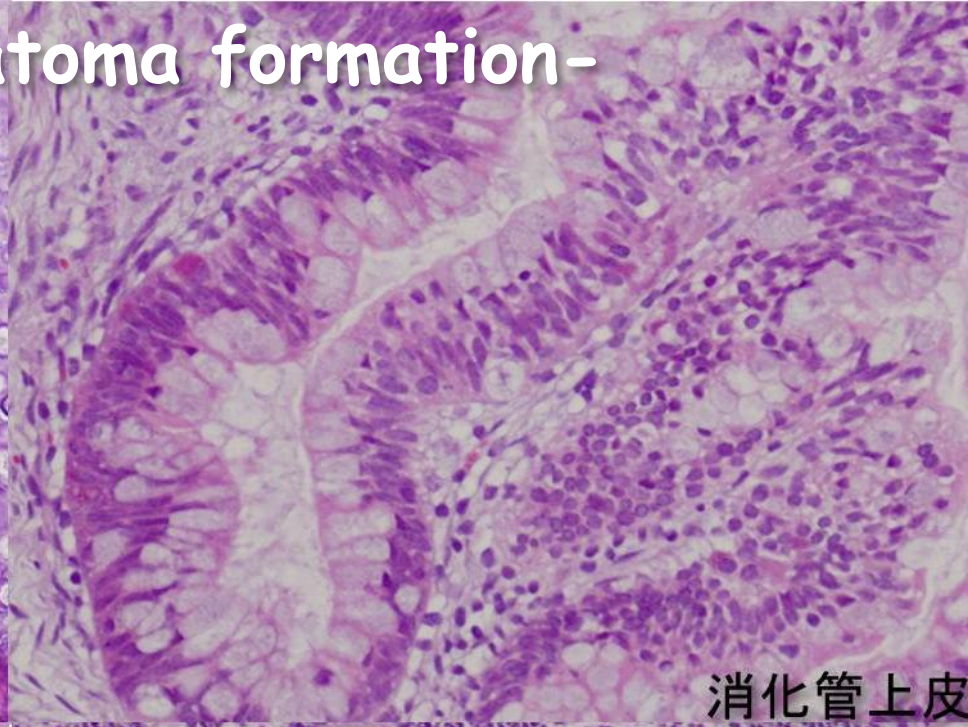

200 µm

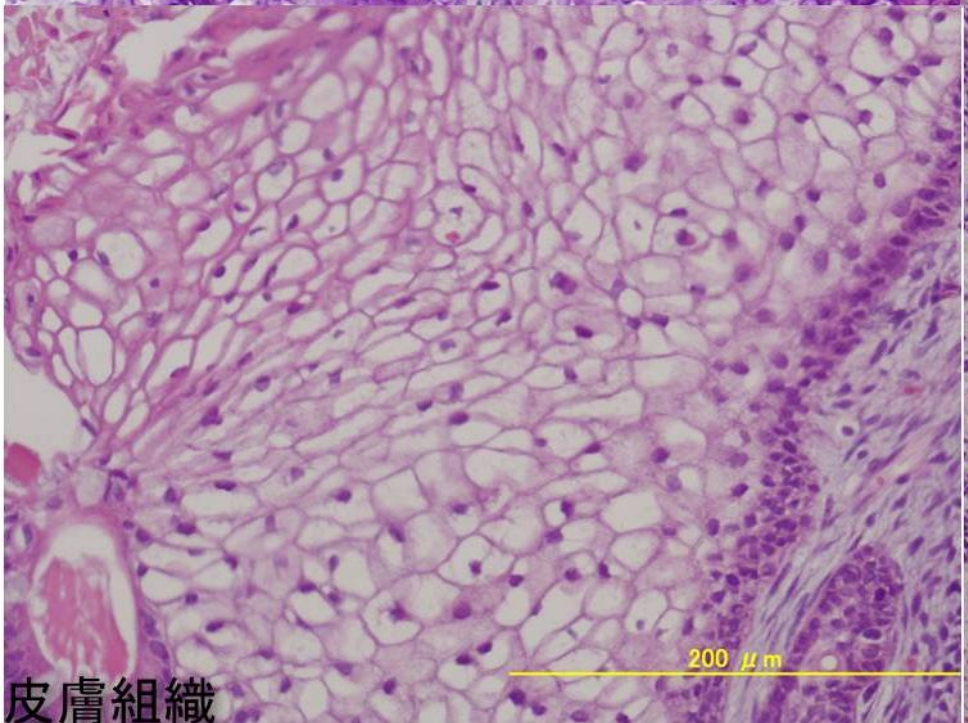
多分化能-Teratoma formation-

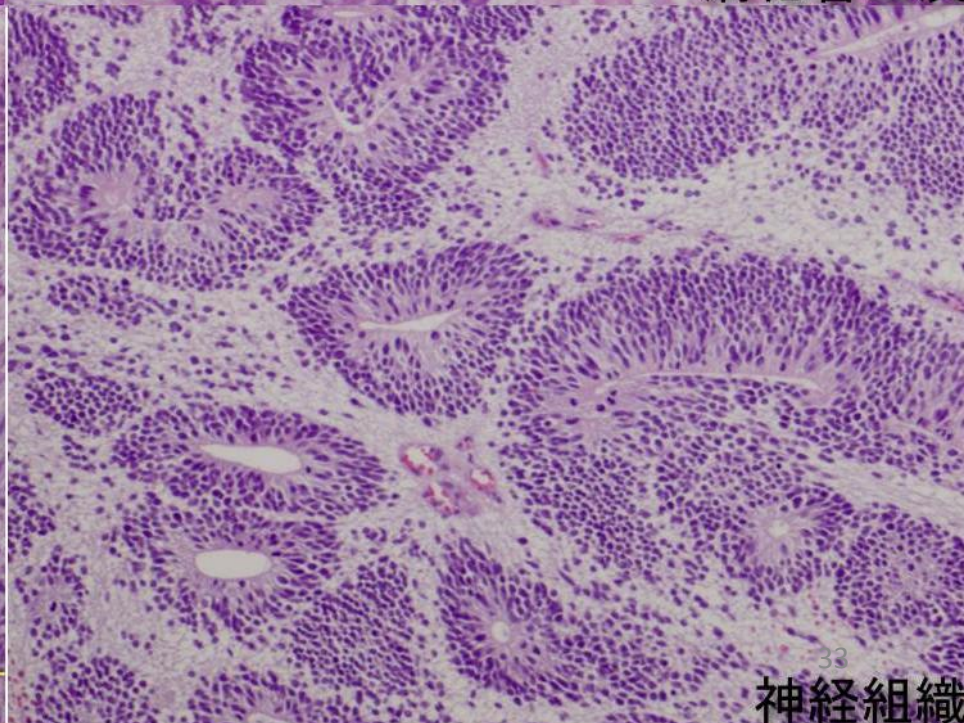


多分化能性-Teratoma formation-

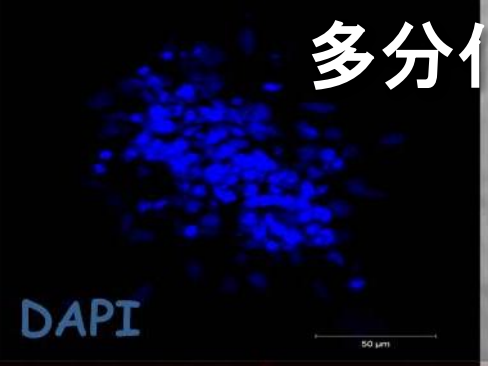


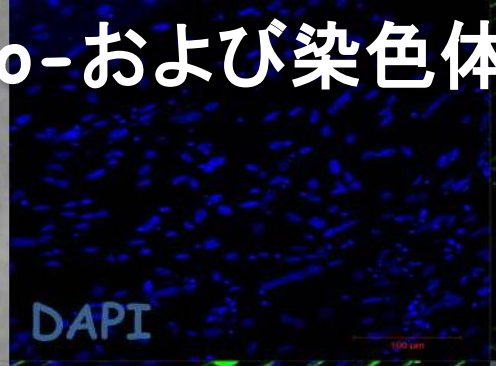


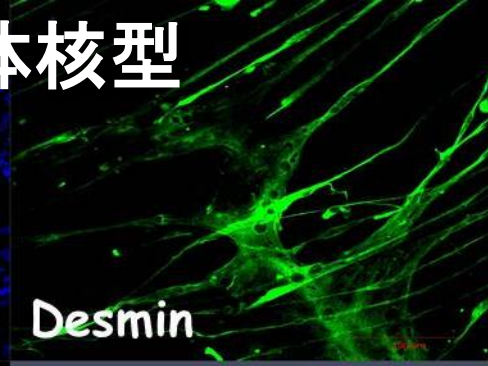


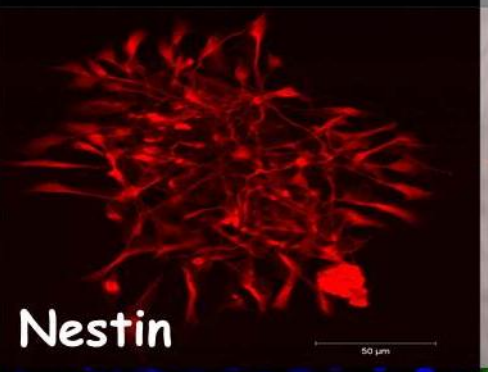


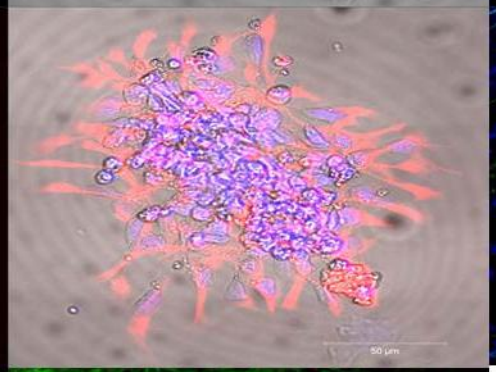
多分化能性-in vitro-および染色体核型

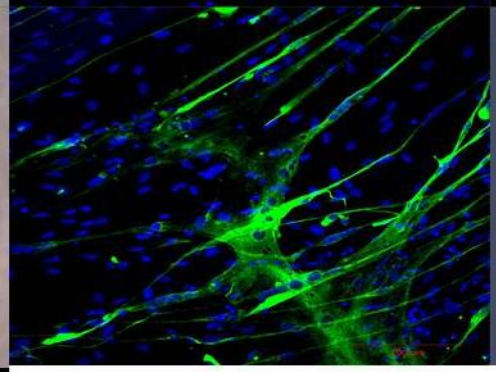


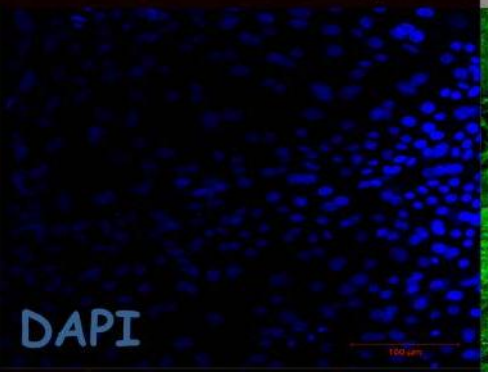


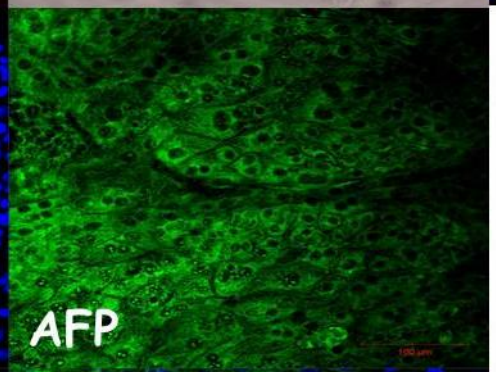


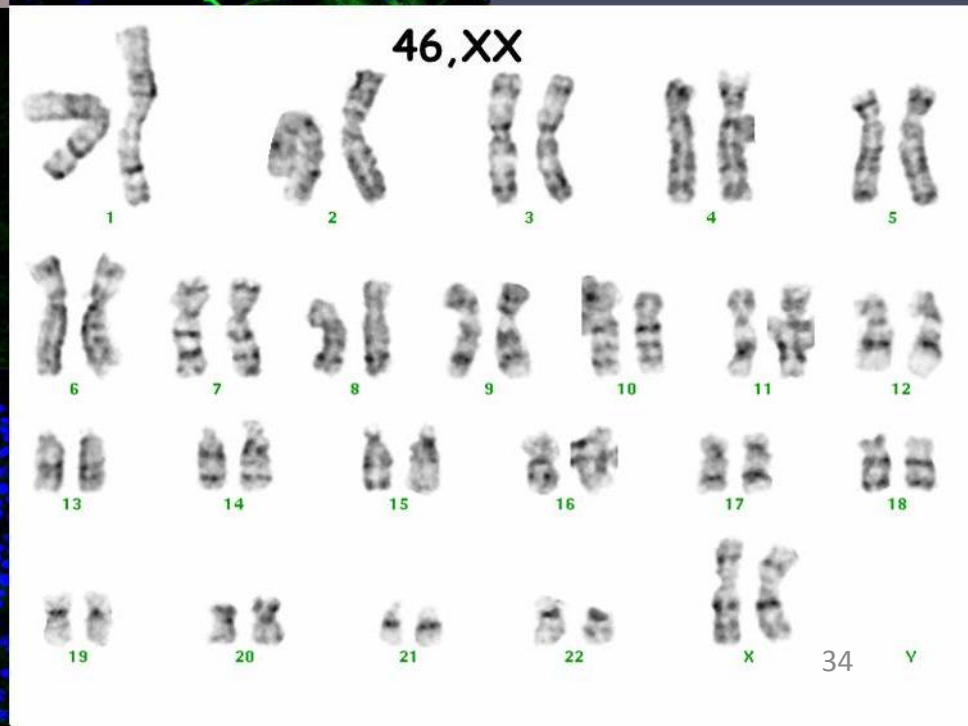


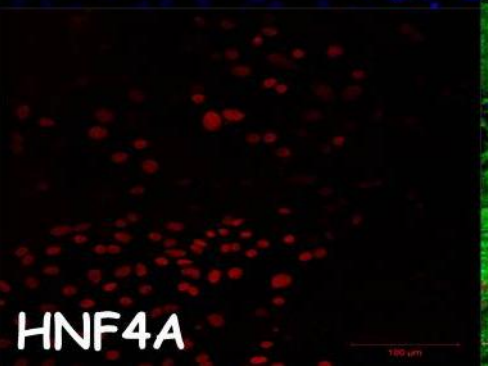




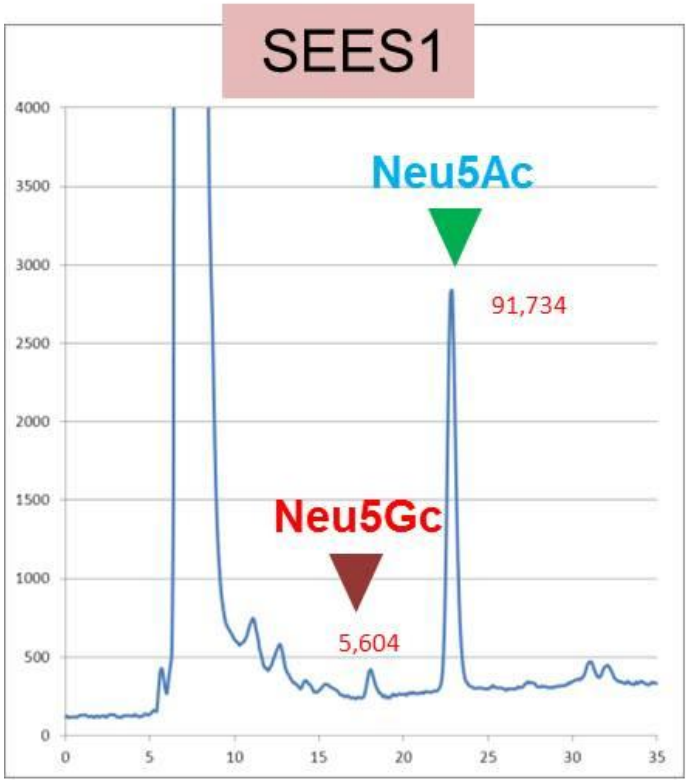


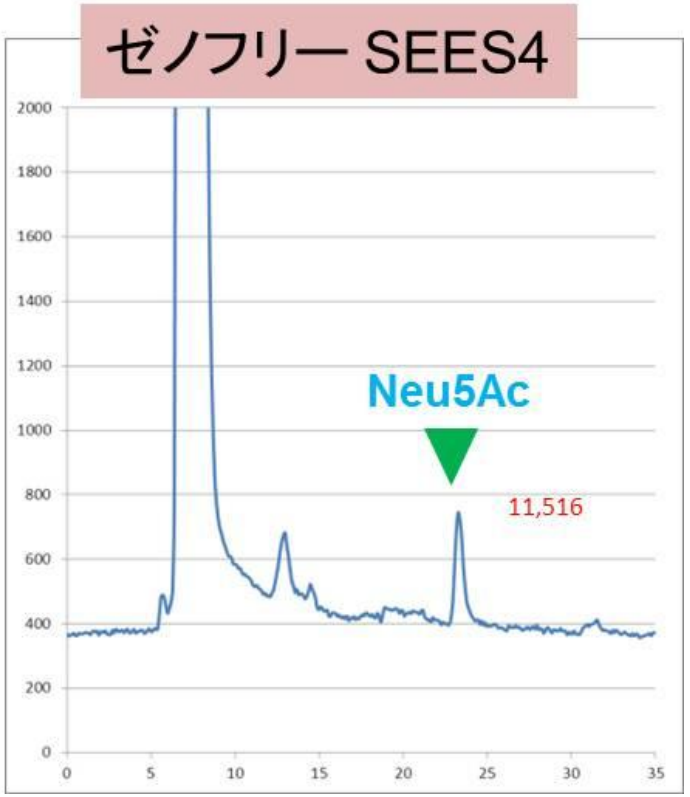






ヒトES細胞非ヒト型シアル酸解析





異種成分に一切触れていないES細胞の樹立