

# 幹細胞之細胞生物學基礎與醫學應用

## The cell biology fundamentals and medical application potentials of stem cells

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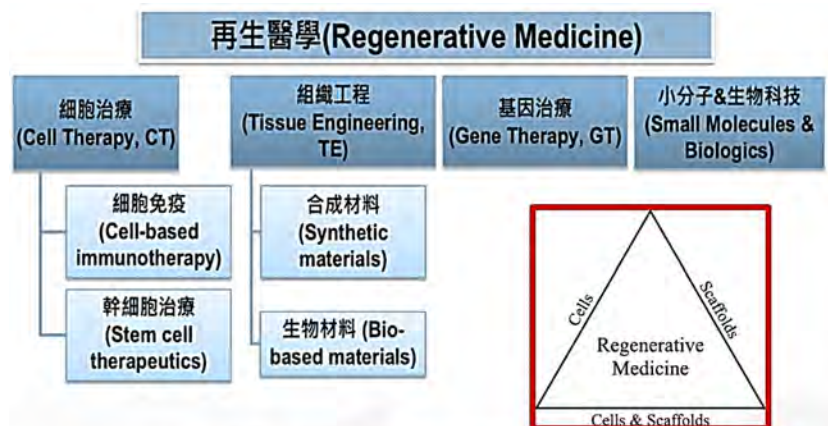
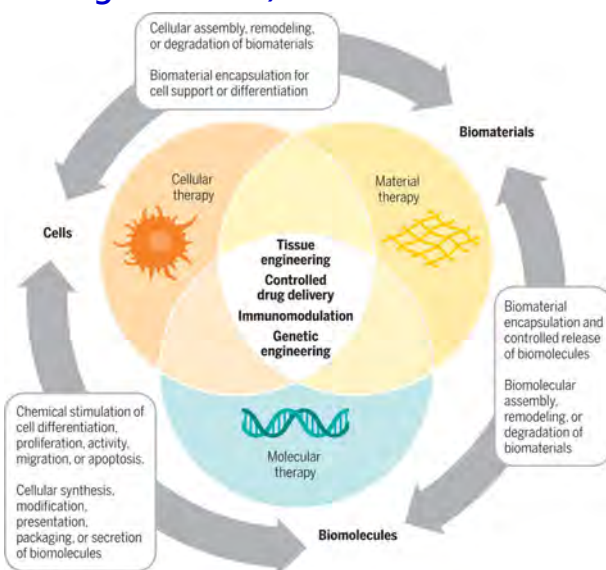
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### 再生醫學與幹細胞治療

- 再生醫學的目標是透過重新製造具有功能之器官組織來修補或取代體內因老化或疾病而受損的器官與組織(Regenerative medicine is a new strategy of therapeutics to restore the functions of damaged tissues) · 再生醫學可透過結合**幹細胞治療**方式進行

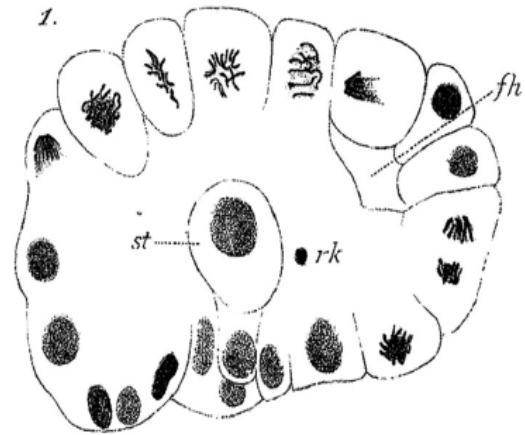


資料來源：工研院IEK ITIS研究團隊整理(2017/04)

圖一 再生醫學之細胞治療範疇與定義

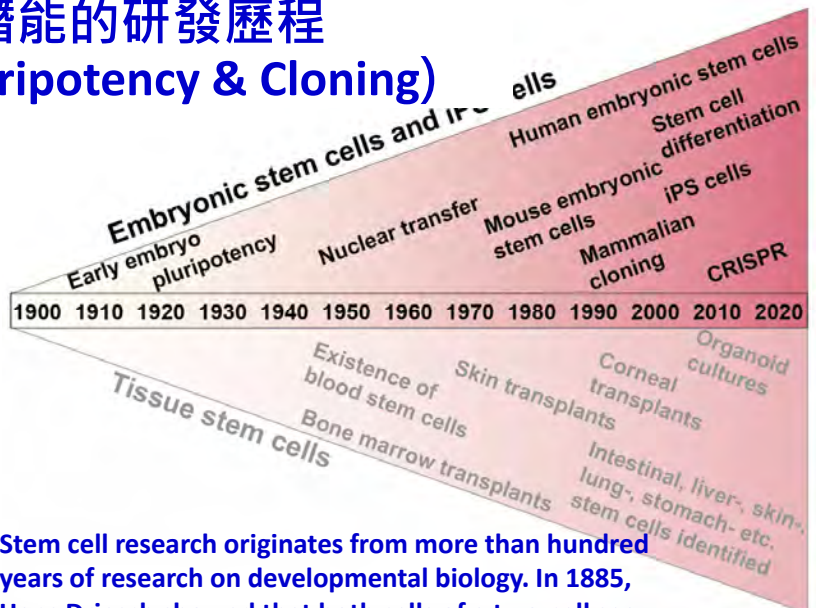
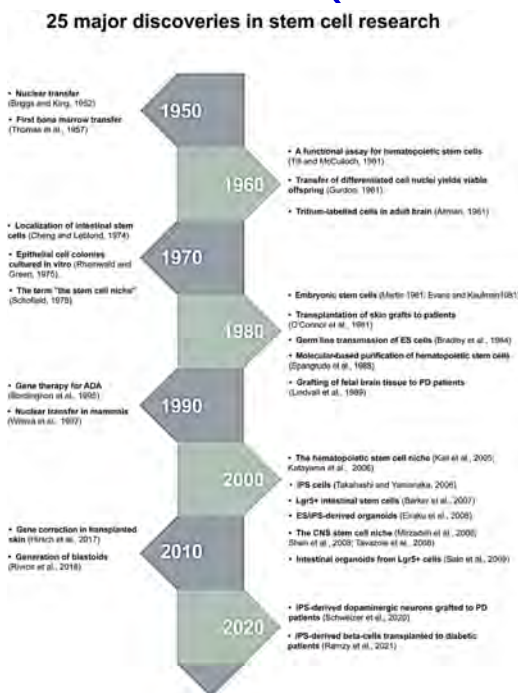
# 什麼是幹細胞?

- ◆ The term “stem cell” appears in the scientific literature as early as 1868 in the works of the eminent German biologist Ernst Haecke
- ◆ Historically, the word *stammzelle* (German for stem cell) had a dual meaning:
  - (1) the evolutionary **unicellular ancestor of multicellular organisms**, and
  - (2) the second being the **ancestral (ontological) stem cell of a tissue** in an organism, initially in the germ line.
 Subsequently, the term became more widely applied to other tissues.



Nature Reports Stem Cells | doi:10.1038/stemcells.2009.90 ; Ramalho-Santos and Willenbring Cell Stem Cells 2007

## 幹細胞潛能的研發歷程 (Stem Cell Pluripotency & Cloning)



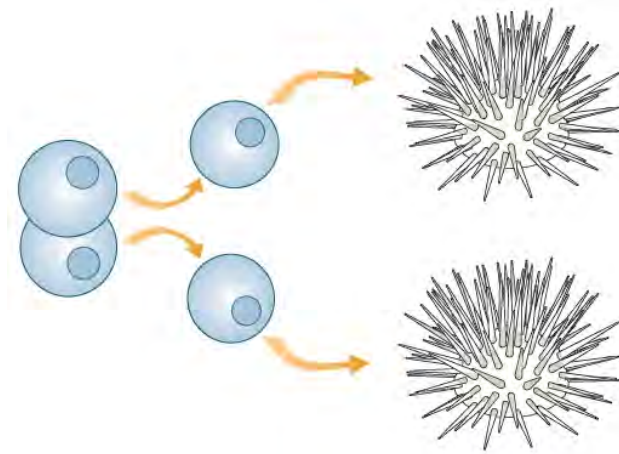
➤ Stem cell research originates from more than hundred years of research on developmental biology. In 1885, Hans Driesch showed that both cells of a two-cell sea urchin embryo are able to develop into a complete sea urchin, demonstrating the totipotency of these cells. Pluripotency of vertebrates (salamanders) was demonstrated by Hans Spemann in similar experiments in the early 20th century

# 幹細胞潛能的研發歷程 (Stem Cell Pluripotency & Cloning)

**Hans Adolf Eduard Driesch 1885 –**

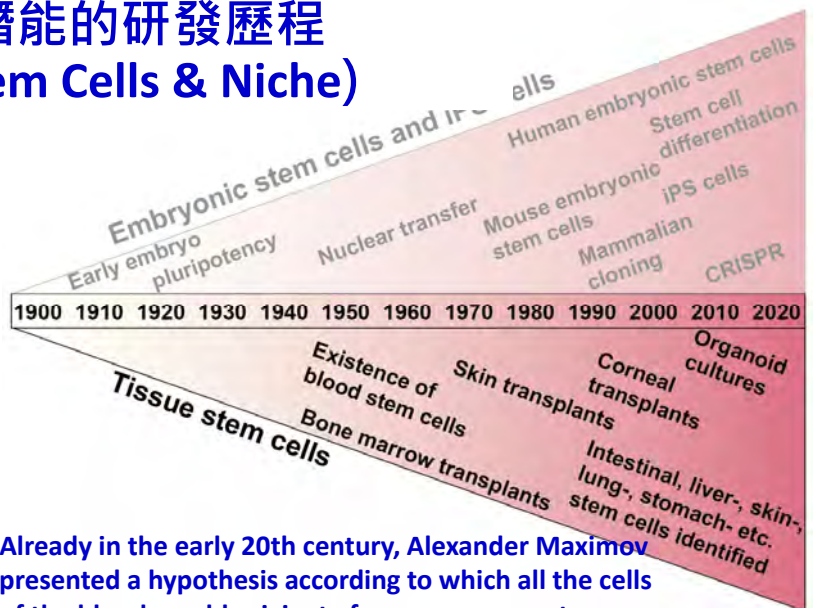
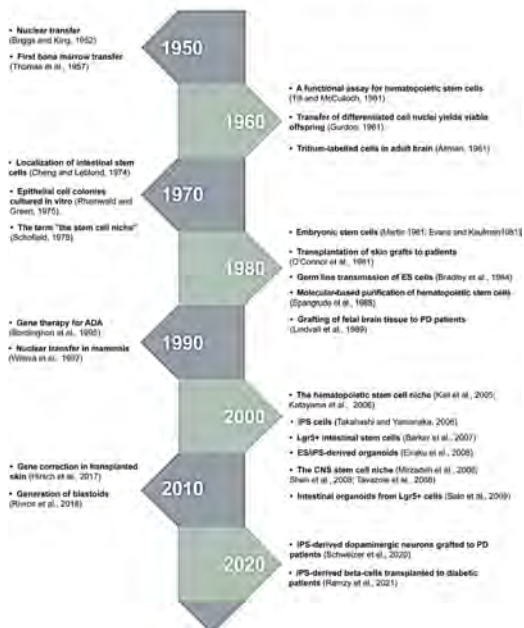
**First-ever demonstration of artificial embryo twinning**

- The sea urchin is a relatively simple organism that is useful for studying development. Driesch showed that by merely shaking two-celled sea urchin embryos, it was possible to separate the cells. Once separated, each cell grew into a complete sea urchin.
- This experiment showed that each cell in the early embryo has its own complete set of genetic instructions and can grow into a full organism.



# 幹細胞潛能的研發歷程 (Tissue Stem Cells & Niche)

**25 major discoveries in stem cell research**

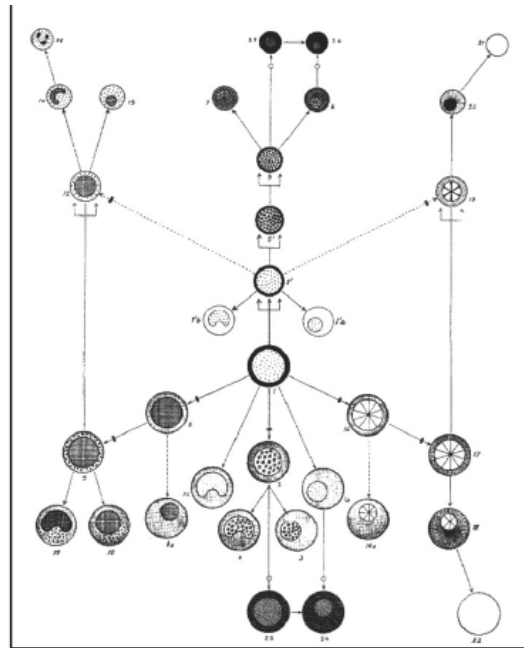


- Already in the early 20th century, Alexander Maximov presented a hypothesis according to which all the cells of the blood would originate from a common stem cell. Half a century later, in the early 1960's, James Till and Ernest McCulloch demonstrated the existence of blood stem cells in experiments where they transplanted bone marrow to mice, whose own bone marrow had been destroyed by irradiation.

## 什麼是幹細胞?

◆ Alexander Maximow (Maximow, 1908), Wera Dantschakoff (Dantschakoff, 1908), Ernst Neumann (Neumann, 1912), and others began to **use the term stem cell to refer to the common precursor of the blood system.**

◆ **The demonstration of the existence of hematopoietic stem cells** (Becker et al., 1963; Till and McCulloch, 1961; Till et al., 1964) established these cells as the prototypical stem cells: (1) cells capable of proliferating nearly indefinitely (**self-renewal**) and (2) of giving rise to specialized cells (**differentiation**).



Nature Reports Stem Cells | doi:10.1038/stemcells.2009.90 ; Ramalho-Santos and Willenbring Cell Stem Cells 2007

## 什麼是幹細胞?

- Stem cells can divide to make more of themselves and generate specialized cell types.
- ✓ **Undifferentiated/unspecialized cells**
- ✓ **Capacity for self-renewal (generally slowly cycling in vivo) which enabled to generate at least one daughter cell (self-renewal capacity)**
- ✓ **Able to undergo multi-lineage differentiation (capable of producing progeny in at least 2 lineages)**
- ✓ **Functional, capable for tissue reconstitution**

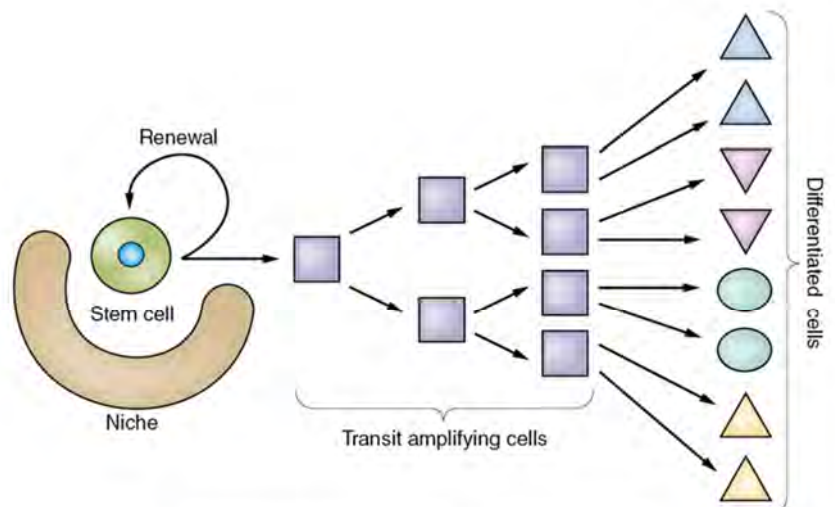
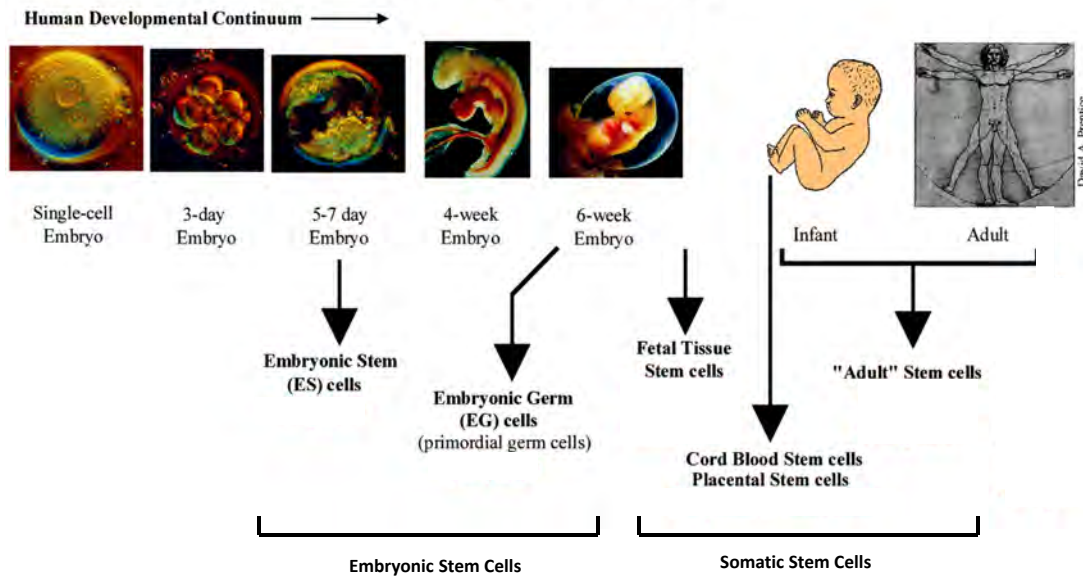


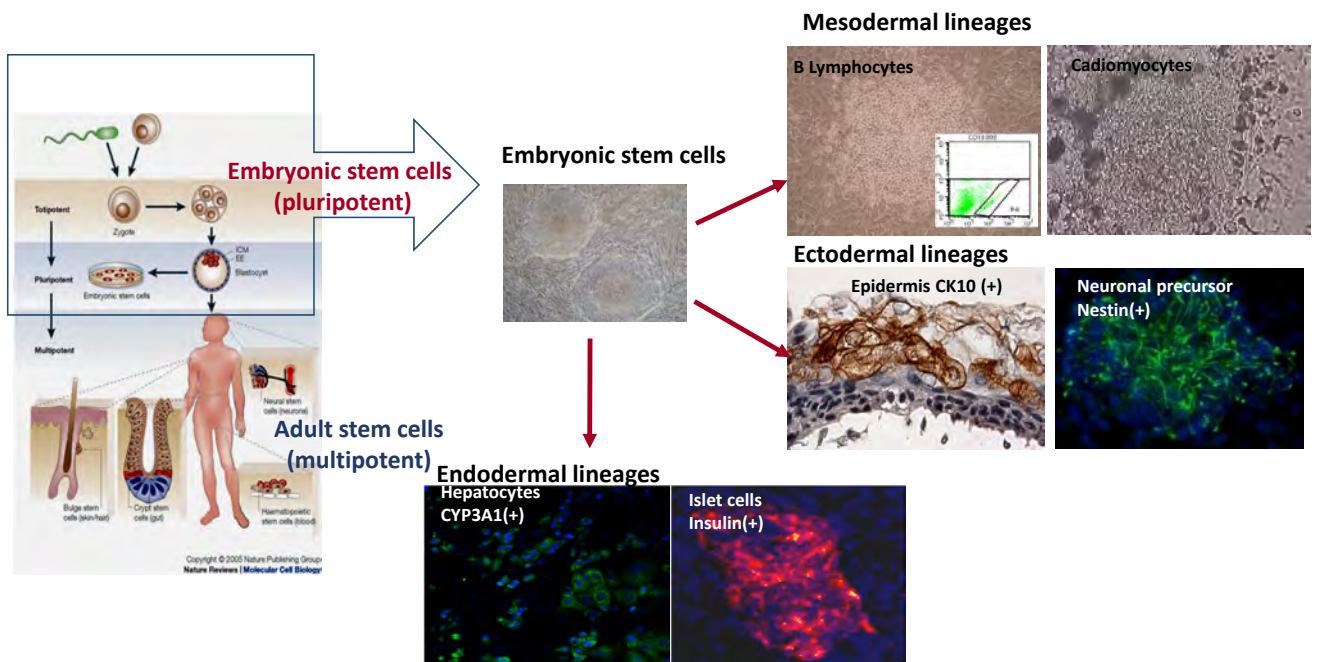
Figure 1.1 A consensus diagram showing stem cell behavior. (Modified from Slack, J.M.W. (2013). *Essential Developmental Biology*, 3rd edn. Reproduced with the permission of John Wiley and Sons.)

# 幹細胞種類



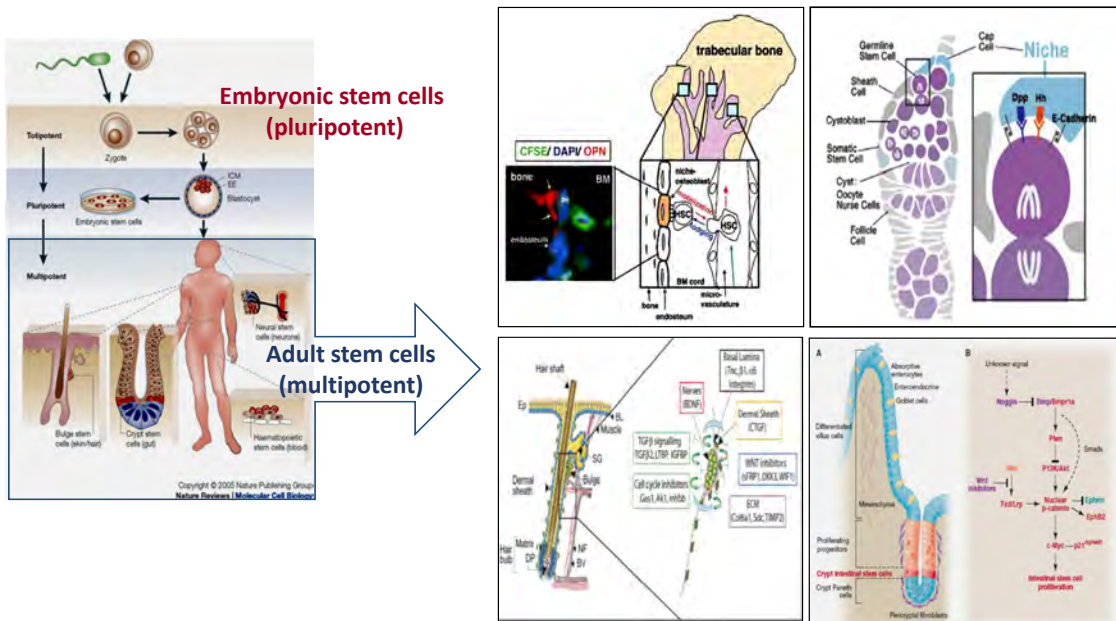
- Two main types: Embryonic stem cells and tissue-specific (adult) stem cells.
- Adult tissue stem cells reside in a niche that expressed specific features

# 胚(胎)幹細胞



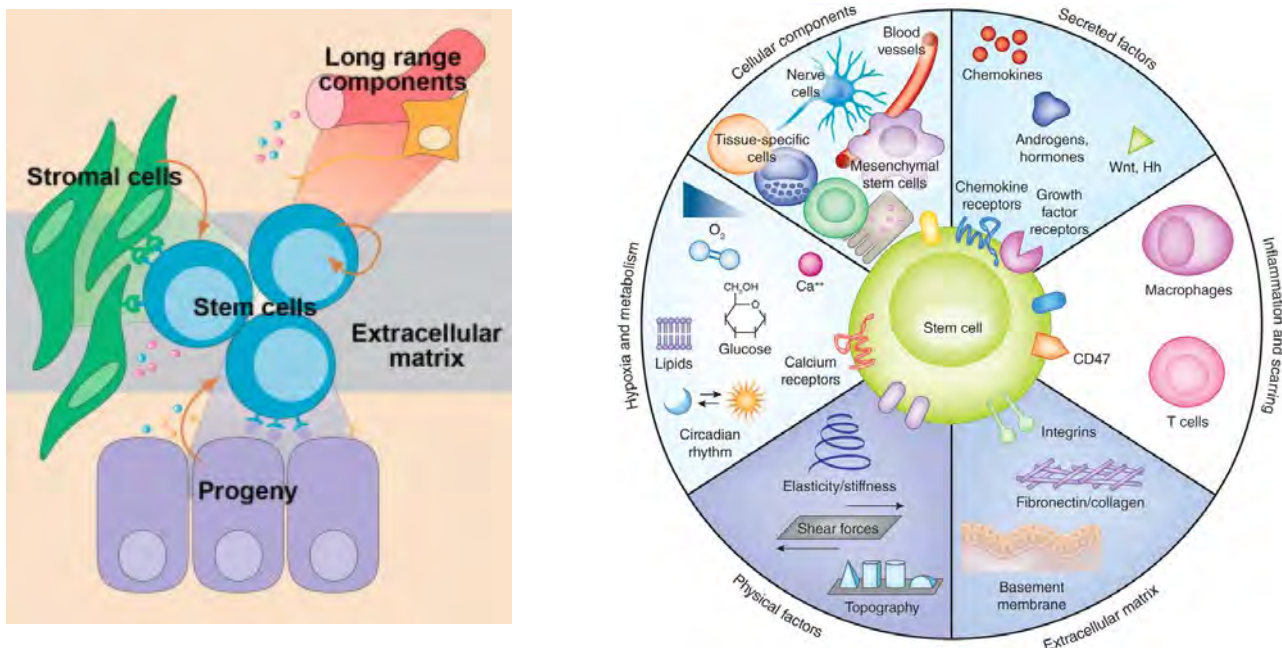
# 成體組織幹細胞

- Tissue stem cells reside in a niche that expressed specific features



# 成體組織幹細胞與幹細胞微環境

- Tissue stem cells reside in a niche that expressed specific features





# 幹細胞治療的起源

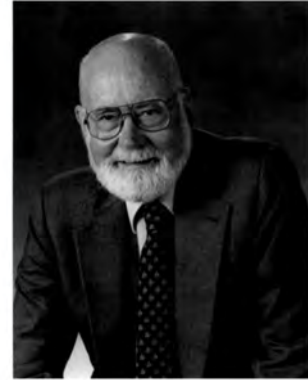
- 1959年Donnall Thomas執行第一例人類骨髓移植並於1990與Joseph E. Murray 因細胞和器官移植的貢獻獲得諾貝爾生醫獎



1990 Nobel Prize

American Journal of Hematology 36:81 (1991)

Congratulations to Dr. E. Donnall Thomas



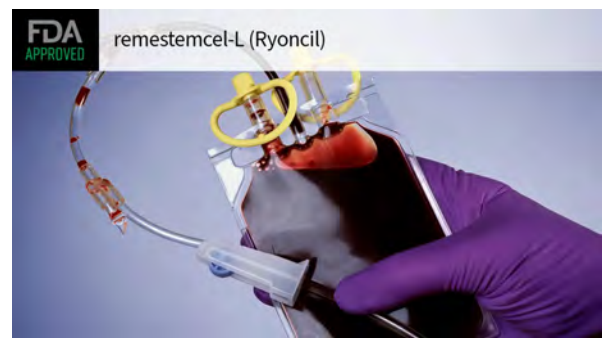
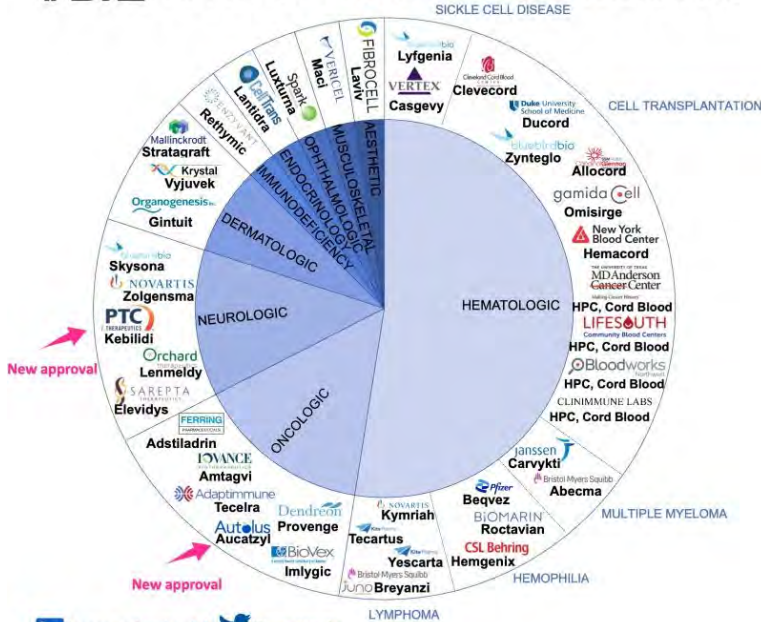
The American Journal of Hematology congratulates editorial board member Dr. E. Donnall Thomas. Dr. Thomas has been awarded the 1990 Nobel Prize in Medicine for his pioneering work in bone marrow transplantation. He shares this year's prize with Dr. Joseph E. Murray, who performed the first successful kidney transplant. Dr. Thomas is an outstanding example of a physician scientist. On behalf of the editorial board, I congratulate Dr. Thomas for this unique honor. —Dr. Ananda S. Prasad © 1991 Wiley-Liss, Inc.

## FDA 核准細胞與基因治療(幹細胞治療)

### FDA APPROVED CELL AND GENE THERAPIES

43 approved cell and gene therapies!

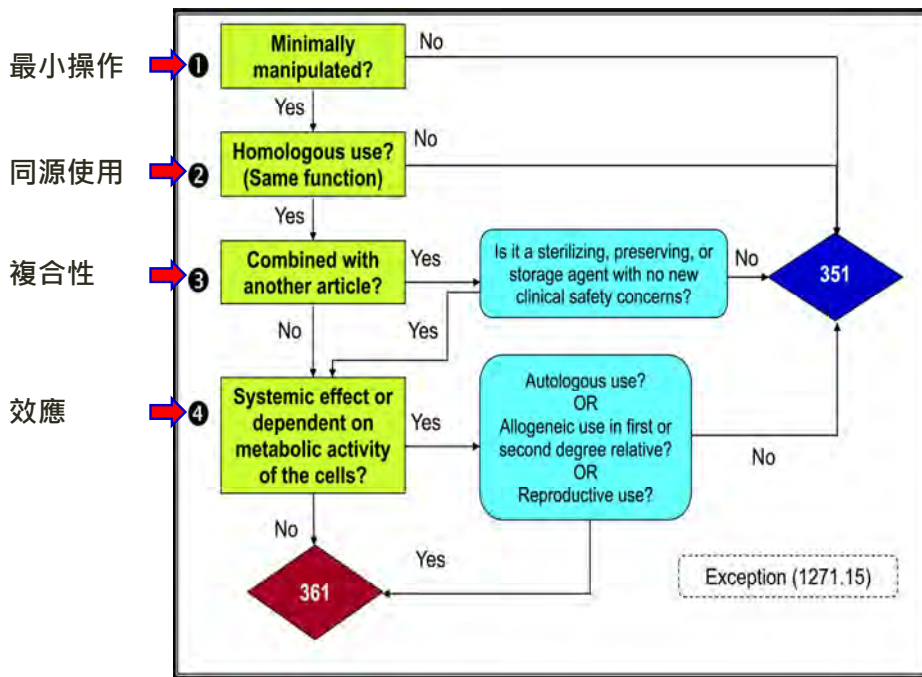
- Last week, The U.S. Food and Drug Administration on Wednesday approved **Mesoblast's** cell therapy for treating a type of complication that occurs after a stem cell or bone marrow transplant called graft-versus-host disease (GVHD). The therapy, branded as Ryoncil, is the first mesenchymal stromal cell therapy approved to treat pediatric patients aged two months and older whose GVHD symptoms have not responded to standard steroid therapy.



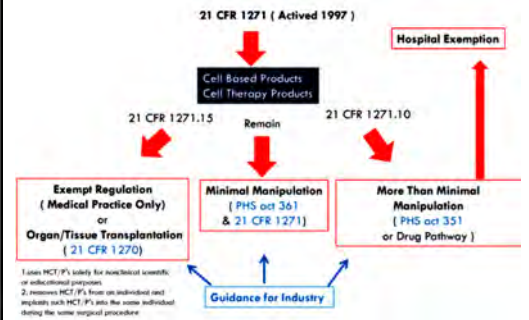
joanna-sadowska-phd @jmsadowska

Source: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>

# 幹細胞治療的風險與FDA法規管理原則



	361 HCT/P	351 HCT/P	
	Tissue	Biologic Therapeutics	Device
Applicable Laws	361 PHS Act	361 PHS Act, 351 PHS Act, FD&C Act	FD&C Act
Applicable Regulations	21 CFR 1271	21 CFR 1271, 21 CFR 600's, 21 CFR 200's, 21 CFR 300's	21 CFR 800's
Marketing Pathway	Premarket review not required	BLA	PMA, 510(k), HDE

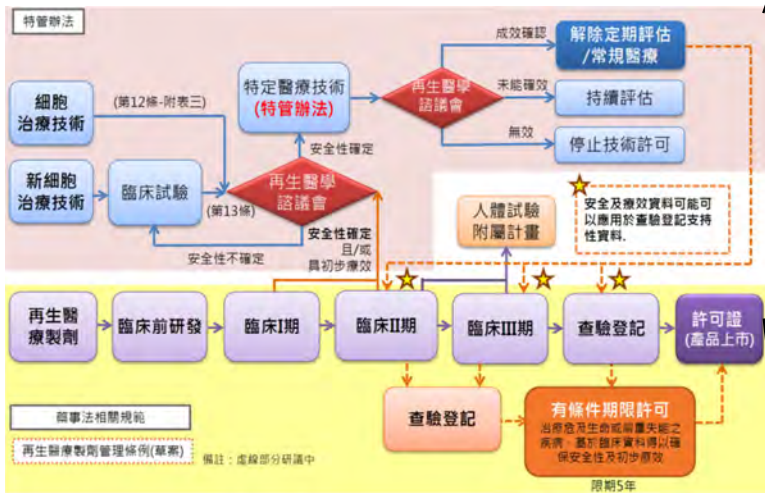


Cytherapy 2019; DOI: 10.1016/j.jcyt.2019.04.002

# 幹細胞治療的風險與法規管理原則



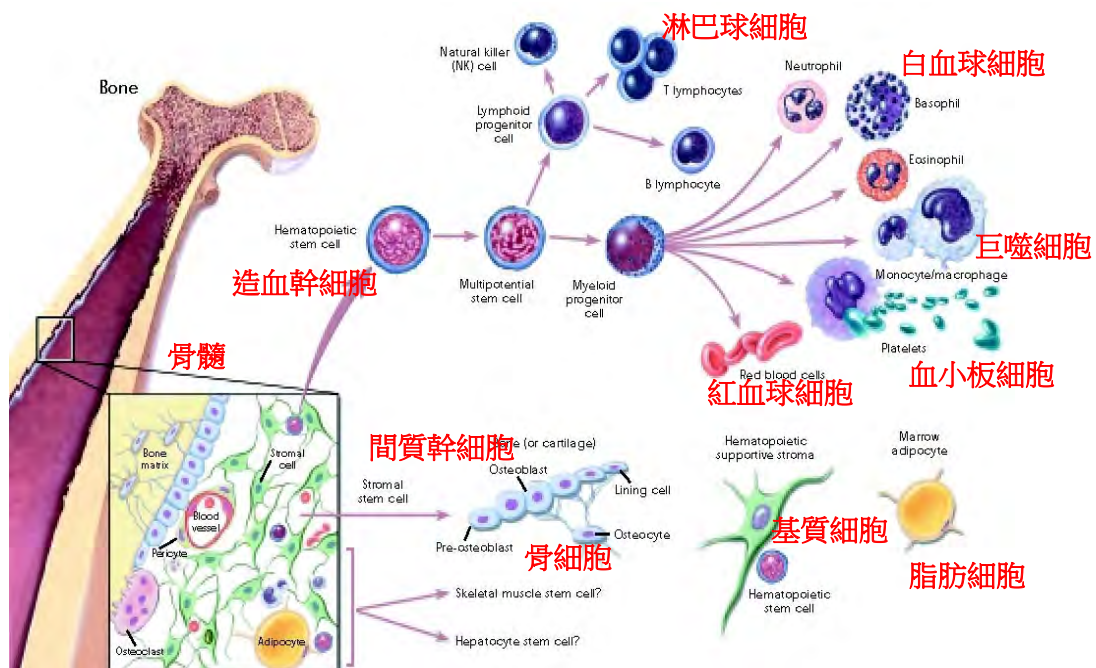
# 細胞治療特管辦法



項目	適應症	申請案件數	申請案件小計	核准案件數		核准案件小計
				執行中	已截止	
自體CD34+ selection	慢性缺血性胸中風	0	0	0	0	0
	膝部下肢缺血症	0	0	0	0	0
自體免疫細胞治療	血液癌症經標準治療無效	14	362	7	2	274
	第一期至第三期實體癌，經標準治療無效	85		48	3	
	實體癌第四期	263		169	45	
自體脂肪幹細胞治療	慢性或滿六週未癒合之閉鎖傷口	39	132	29	2	89
	占總體表面積百分之二十以上之大面積燒傷或皮膚創傷受瘻	1		0	0	
	皮下及軟組織缺損	25		8	3	
	退化性關節炎及膝關節軟骨缺損	67		46	1	
自體纖維母細胞治療	皮膚缺陷：皺紋、凹洞及疤痕之填補及修復	17	17	13	2	15
自體骨髓間質幹細胞治療	退化性關節炎及膝關節軟骨缺損	17	38	7	6	31
	脊髓損傷	21		11	7	
自體軟骨細胞治療	膝關節軟骨缺損	12	12	10	1	11
非附表三細胞治療技術		23	23	0	0	0
總計			584	420		

項目	適應症	已核准計畫 (單位/件數)	總受案人次* (單位/人次)
自體免疫細胞治療	血液癌症經標準治療無效 第一至第三期實體癌，經標準治療無效 實體癌第四期	274	1442
自體脂肪幹細胞治療	退化性關節炎及膝關節軟骨缺損 慢性或滿六週未癒合之困難傷口	89	179
自體纖維母細胞治療	皮膚缺陷：皺紋、凹洞及疤痕之填補及修復	15	13
自體骨髓間質幹細胞治療	脊髓損傷	31	92
	退化性關節炎及膝關節軟骨缺損		
自體軟骨細胞治療	膝關節軟骨缺損	11	64
總計		420	1790

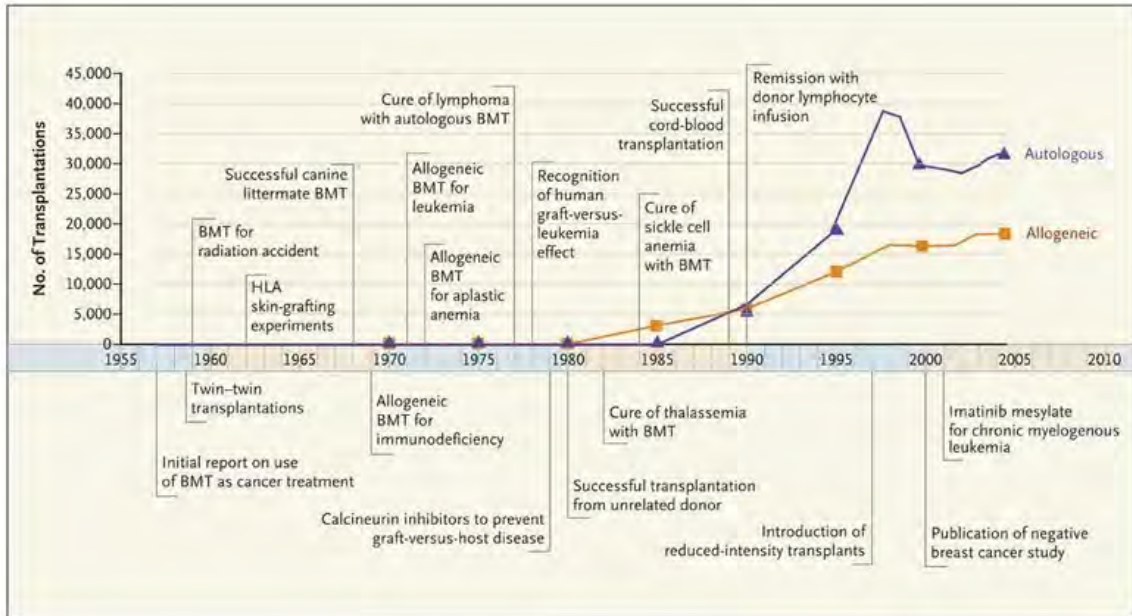
# 骨髓間造血幹細胞



NIH Stem Cells

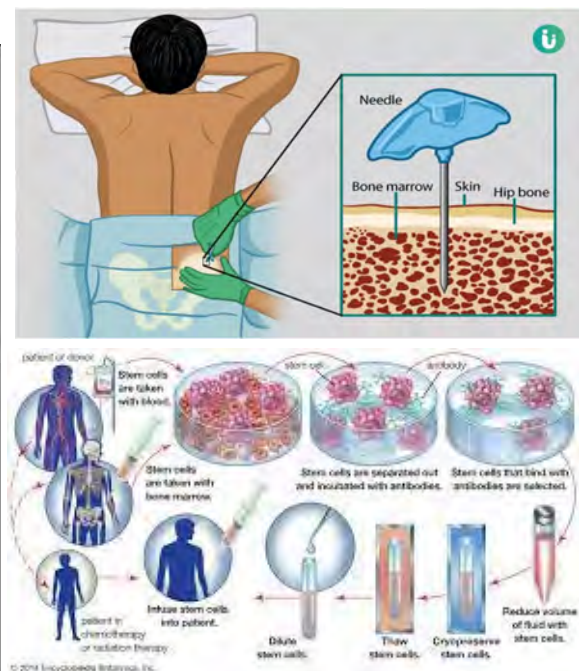
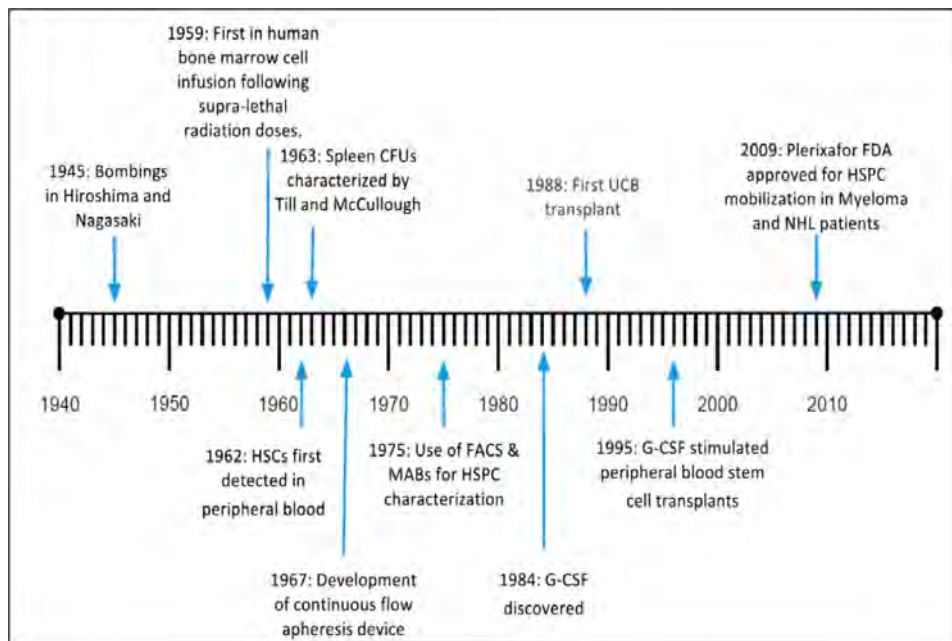
# 骨髓移植的臨床運用

- **Bone marrow transplantation:** A bone marrow transplant involves taking cells that are normally found in the bone marrow (stem cells), filtering those cells, and giving them back either to the donor (patient) or to another person



N Engl J Med 2007; 357:1472-1475 DOI: 10.1056/NEJMp078166

# 造血幹細胞治療的臨床應用

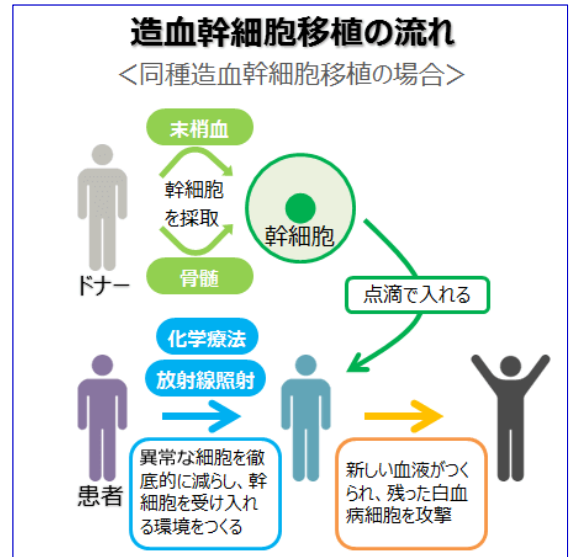
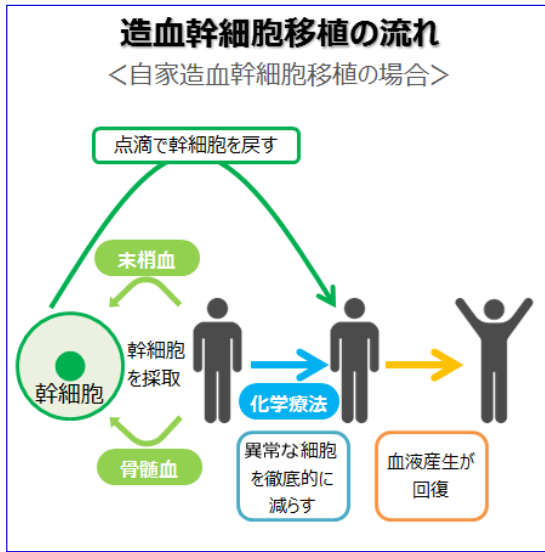


# 造血幹細胞治療的臨床應用

Table 1. Diseases Commonly Treated with Hematopoietic Stem-Cell Transplantation.

<b>Autologous transplantation*</b>	
Cancers	血液腫瘤/淋巴癌
Multiple myeloma	
Non-Hodgkin's lymphoma	
Hodgkin's disease	
Acute myeloid leukemia	
Neuroblastoma	
Ovarian cancer	
Genit-cell tumours	
Other diseases	
Autoimmune disorders	
Amyloidosis	
<b>Allogeneic transplantation†</b>	
Cancers	血液腫瘤/淋巴癌
Acute myeloid leukemia	
Acute lymphoblastic leukemia	
Chronic myeloid leukemia	
Myelodysplastic syndromes	
Myeloproliferative disorders	
Non-Hodgkin's lymphoma	
Hodgkin's disease	
Chronic lymphocytic leukemia	
Multiple myeloma	
Juvenile chronic myeloid leukemia	
Other diseases	
Aplastic anemia	血液疾病/貧血
Paroxysmal nocturnal hemoglobinuria	
Fanconi's anemia	
Blackfan-Diamond anemia	
Thalassemia major	
Sickle cell anemia	
Severe combined immunodeficiency	
Wiskott-Aldrich syndrome	
Inborn errors of metabolism	

\* More than 30,000 autologous transplantations are performed annually worldwide, two thirds for multiple myeloma or non-Hodgkin's lymphoma.  
 † More than 15,000 allogeneic transplantations are performed annually worldwide, nearly half for acute leukemias. The vast majority are performed to treat lymphoid and hematologic cancers.

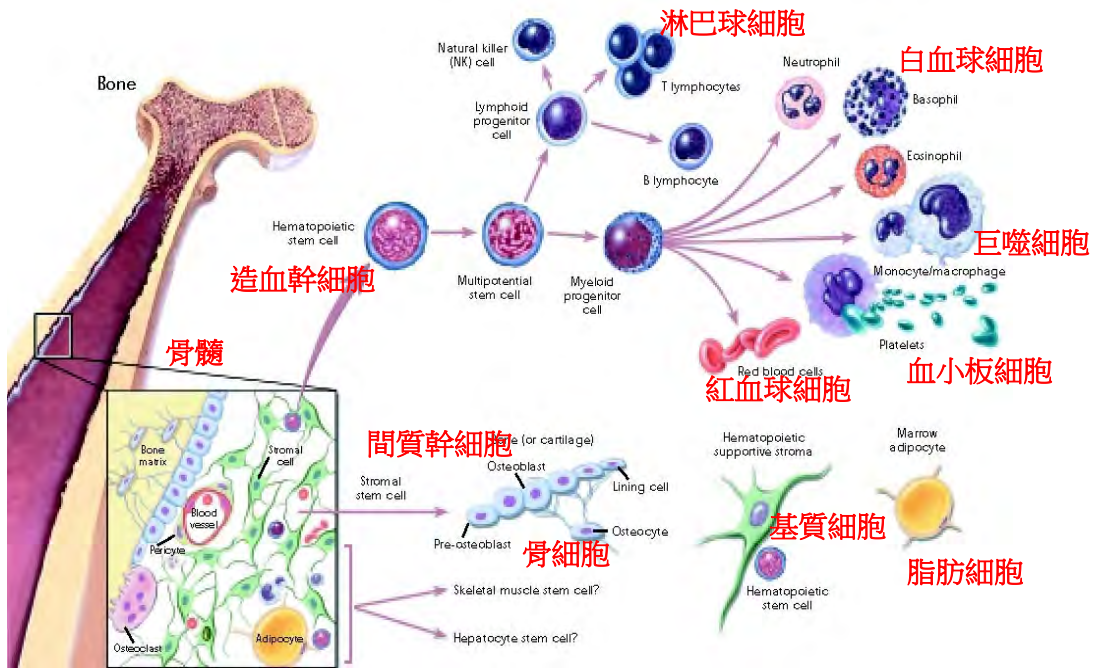


Coplan EA. N Engl J Med 2006;354:1813-1826

## 骨髓與周邊造血幹細胞的臨床應用比較

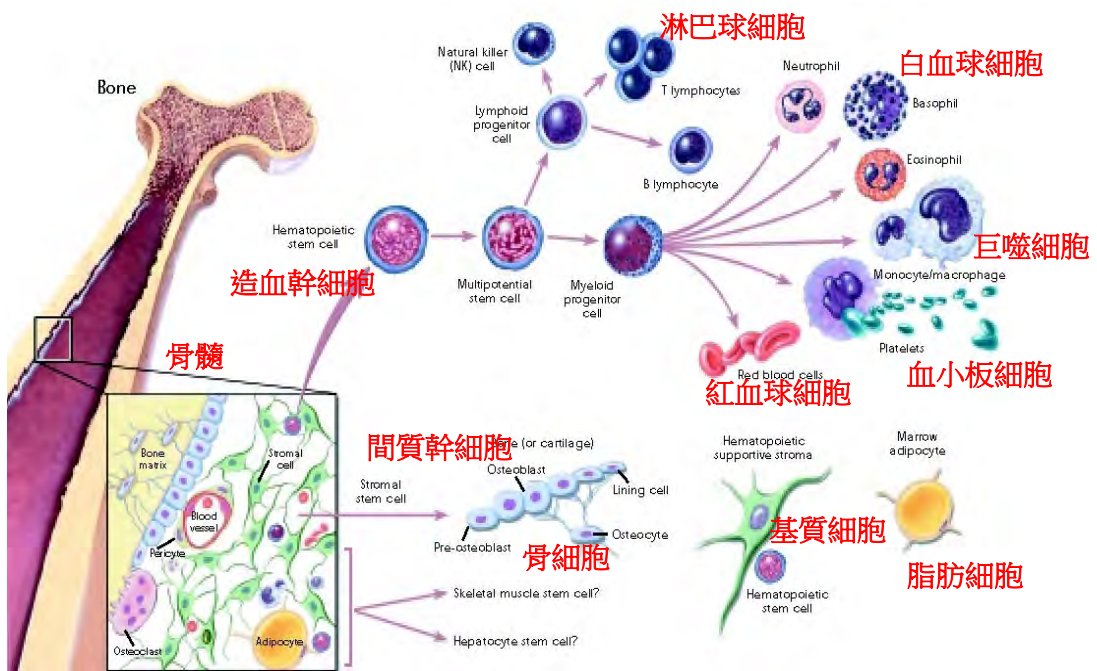
Parameter	Bone Marrow	Cord Blood	Mobilized Peripheral Blood
Engraftment (HSCT)		Slowest engraftment	Rapid engraftment when used for HSCT than bone marrow
Risk of GvHD		Lowest risk of GvHD due to primitive nature of HSPCs	Higher risk of GvHD than bone marrow
Proliferation	30-60% of BM CD34+ cells are in S + G2M phases; fewer in G0/G1 phase	Majority of CB and PB cells are in G0/G1 phase	Majority of CB and PB cells are in G0/G1 phase
Marker Expression			Reduced CD117 or c-kit
Response to Cytokine stimulation	No noticeable effect on BM-HSPCs with SCF or IL-3	Stimulation of HSPCs from CB and PB with SCF and IL-3 transiently increased their proliferation in vitro	Stimulation of HSPCs from CB and PB with SCF and IL-3 transiently increased their proliferation in vitro

# 骨髓間質幹細胞



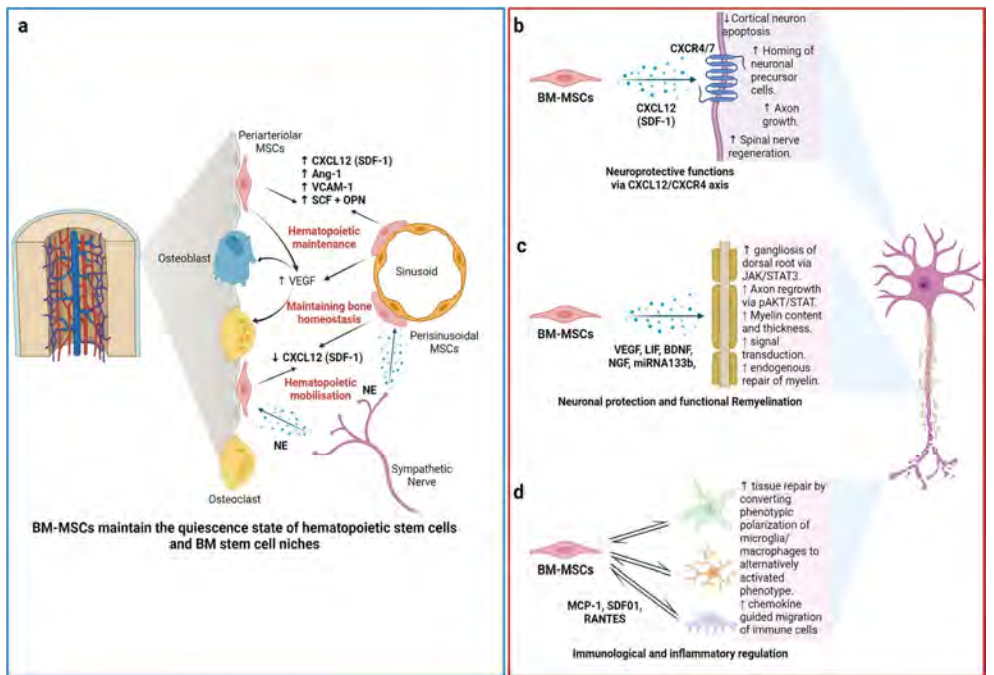
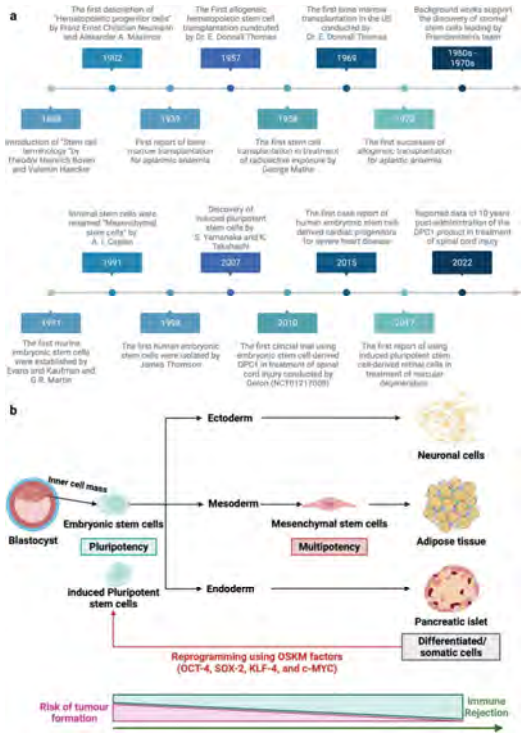
NIH Stem Cells

# 骨髓間質幹細胞



NIH Stem Cells

# 骨髓間質幹細胞的分離與鑑定



Sig Transduct Target Ther 7, 272 (2022).

# 骨髓間質幹細胞的分離與鑑定

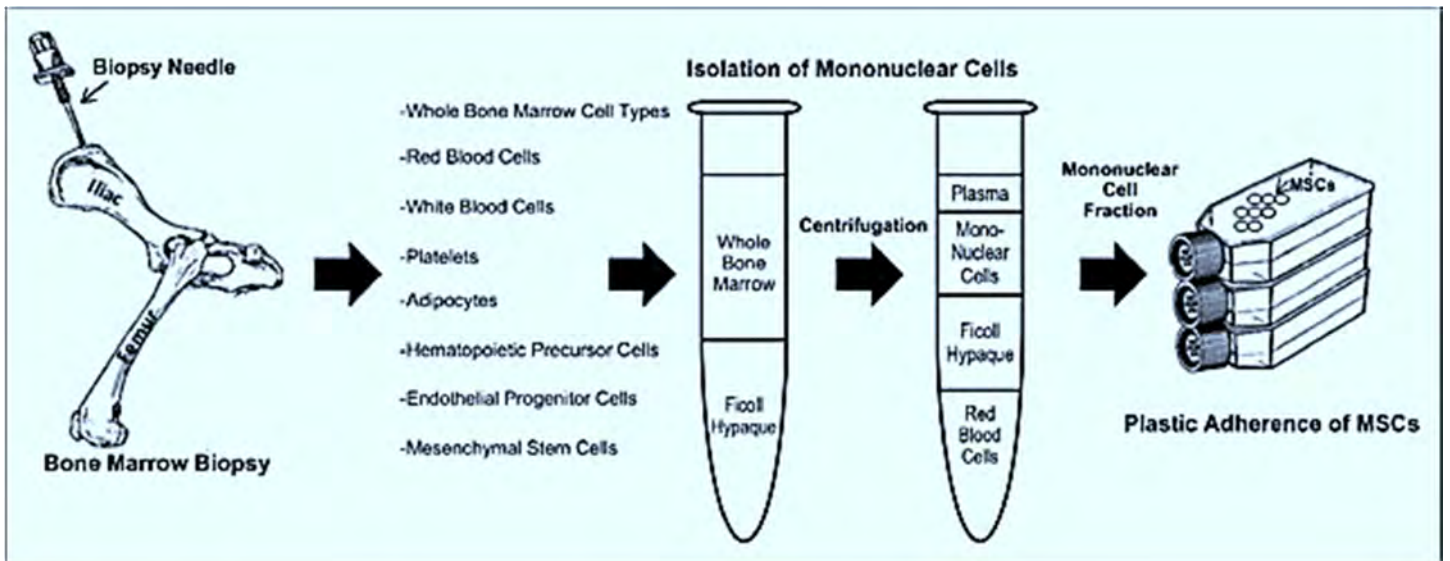
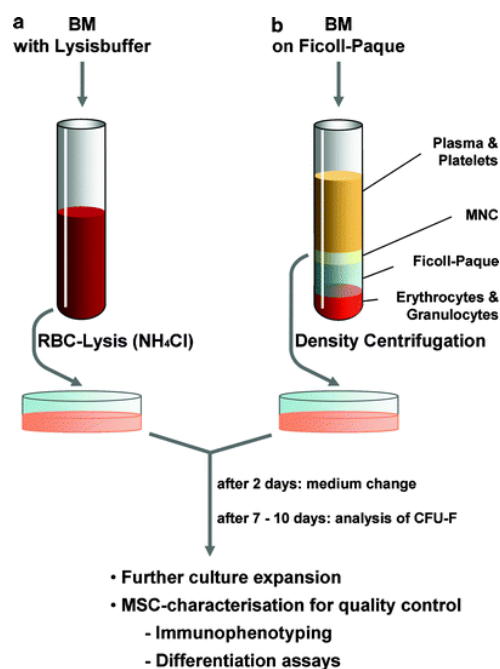


Figure adopt from Williams and Hare

# 骨髓間質幹細胞分離

## Isolation of MSCs from BM aspirate

- BM aspirate is mixed with lysis buffer. When the erythrocytes are lysed, the cell pellet is washed, cells are counted and seeded in culture medium.
- BM aspirate is mixed with PBS and carefully layered on the Ficoll-Paque for density gradient centrifugation. Subsequently, the MNC interphase ring is harvested, the cells are counted and seeded in culture medium.

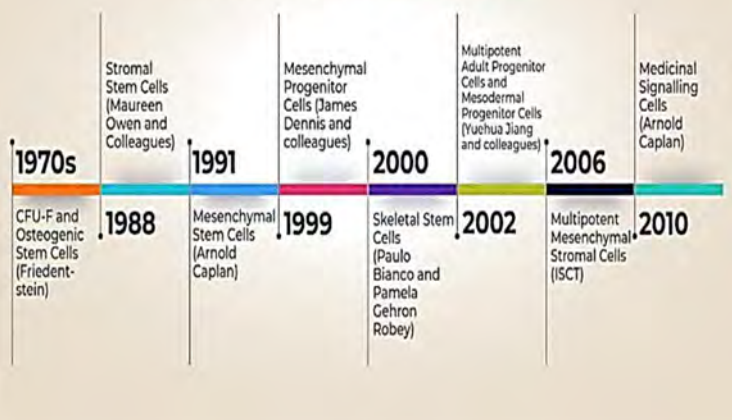


Mesenchymal Stem Cell Assays and Applications pp 23-35

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# 骨髓間質幹細胞的起源與命名

## Nomenclature of Mesenchymal Stem Cells



In 2006, the International Society for Cellular Therapy (ISCT) proposed the term “multipotent mesenchymal stromal cells”, and provided a set of criteria to define human MSCs. These criteria include adherence to plastic in culture, expression of specific surface markers, and the ability to differentiate into osteoblasts, adipocytes, and chondrocytes.

### Colony-Forming Unit-Fibroblasts (CFU-F)

Historically significant term reflecting early isolation and **Mesenchymal Stem Cells**

Coined by Arnold Caplan in 1991 based on their capability to form mesenchymal tissues.

### Multipotent Stem Cells

Reflecting the cells’ ability to differentiate into diverse cell types.

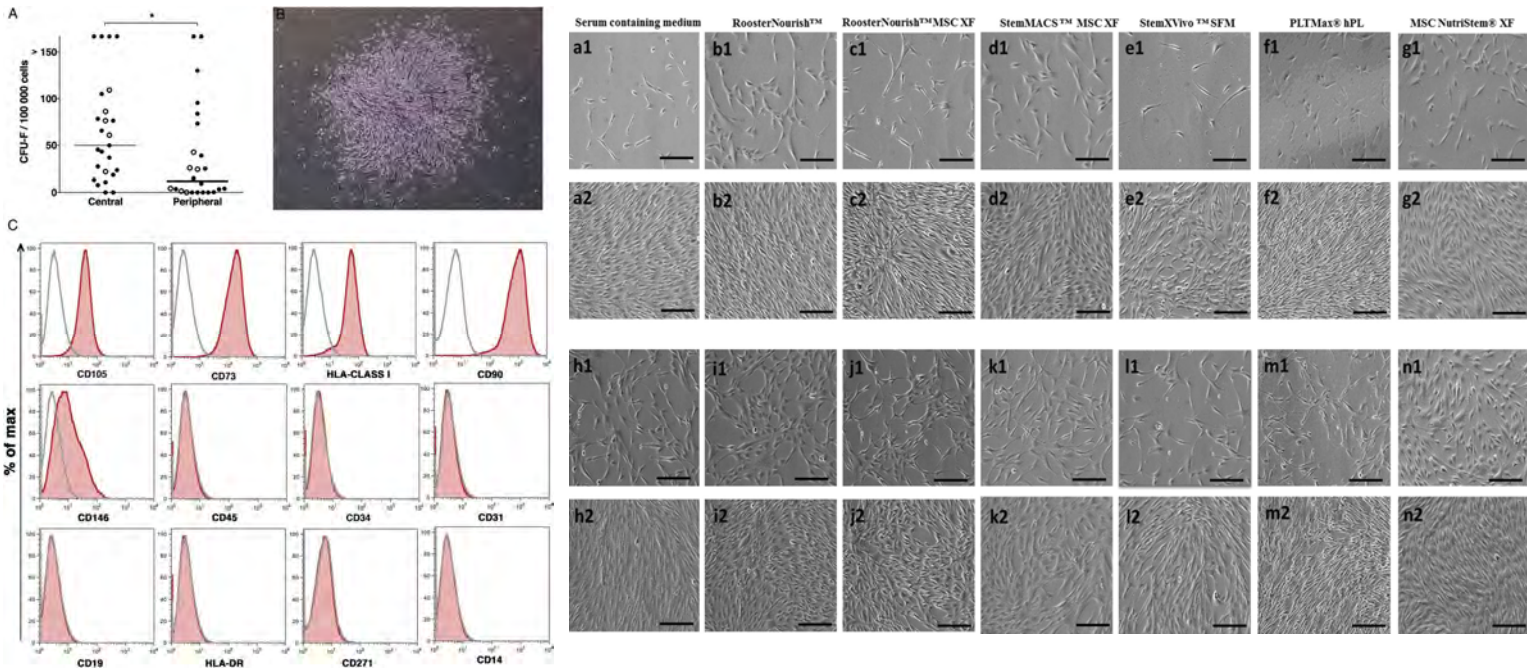
### Mesenchymal Stromal Cells

Acknowledges the challenge of isolating ‘pure’ stem cells, often collected with non-stem cell types from stromal tissue.

### Medicinal Signalling Cells

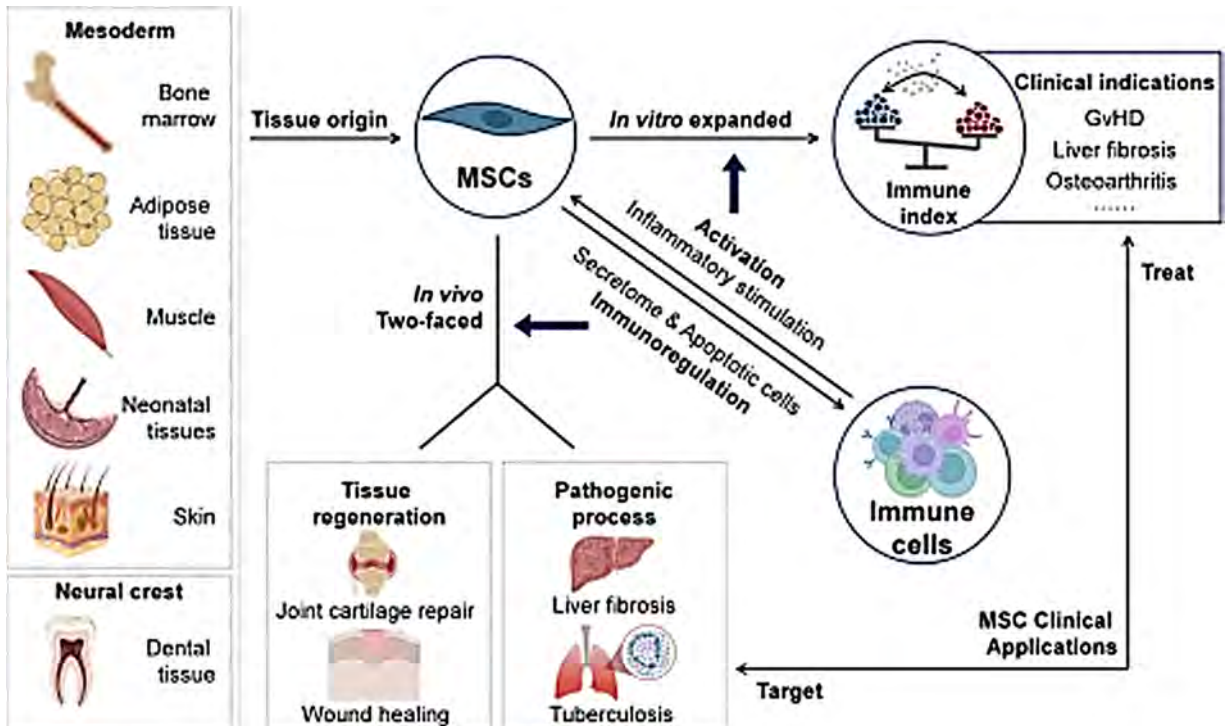
Emphasises MSCs’ therapeutic potential beyond traditional stem cell roles.

# 骨髓間質幹細胞的鑑定



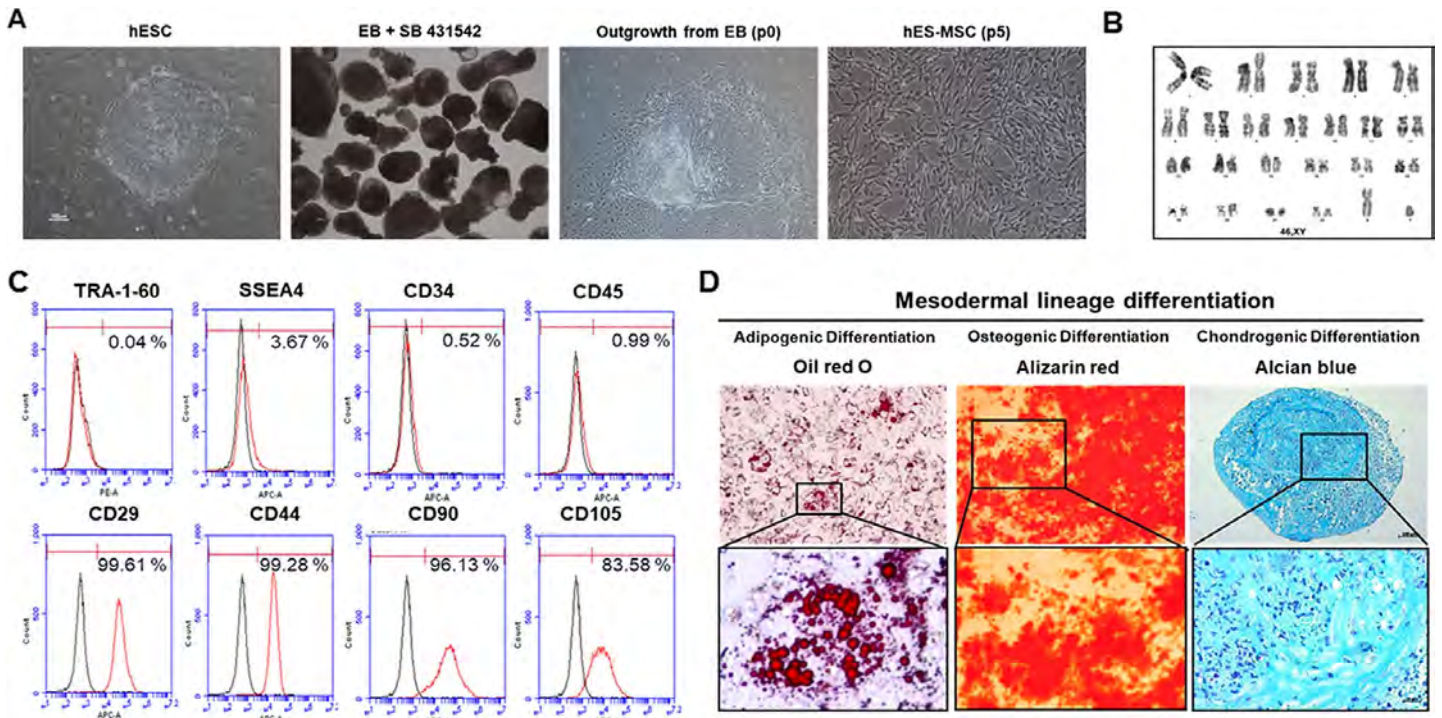
BMJ Open Resp Res (2014); Sci Rep 11, 3403 (2021)

# 間質幹細胞的來源與應用潛能



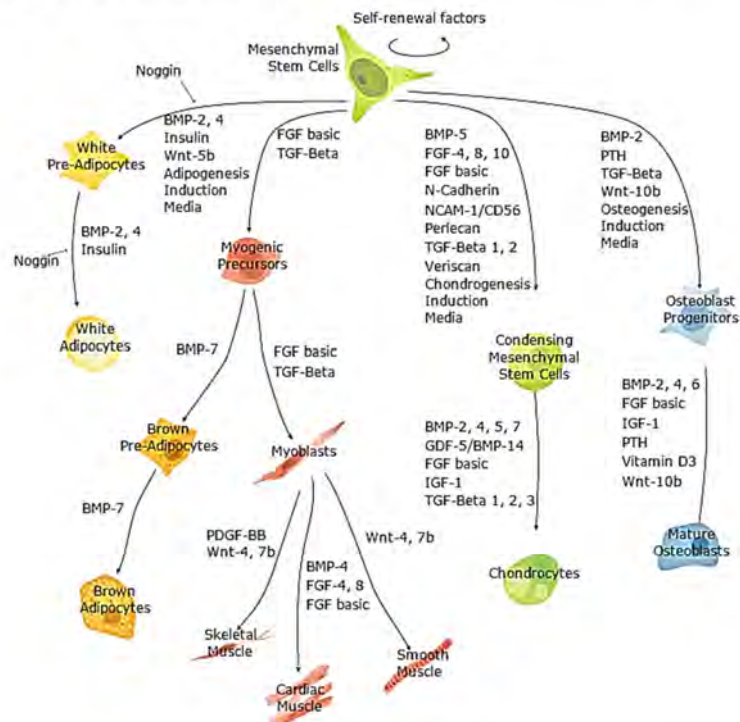
Cell Mol Immunol 20, 555–557 (2023)

# 間質幹細胞的鑑定

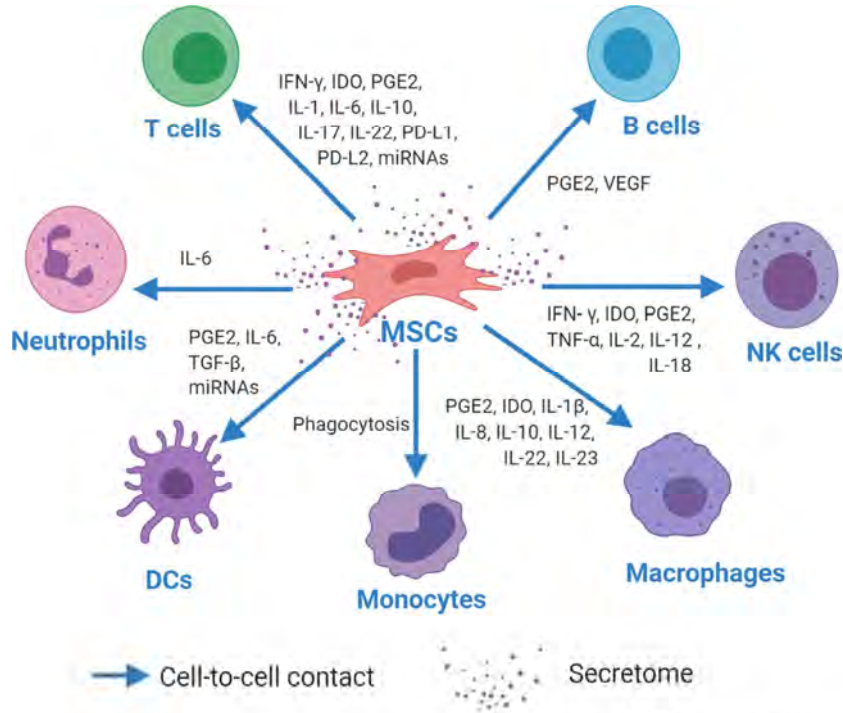


Stem Cell Res Ther 11, 255 (2020).

# 間質幹細胞的分化潛力



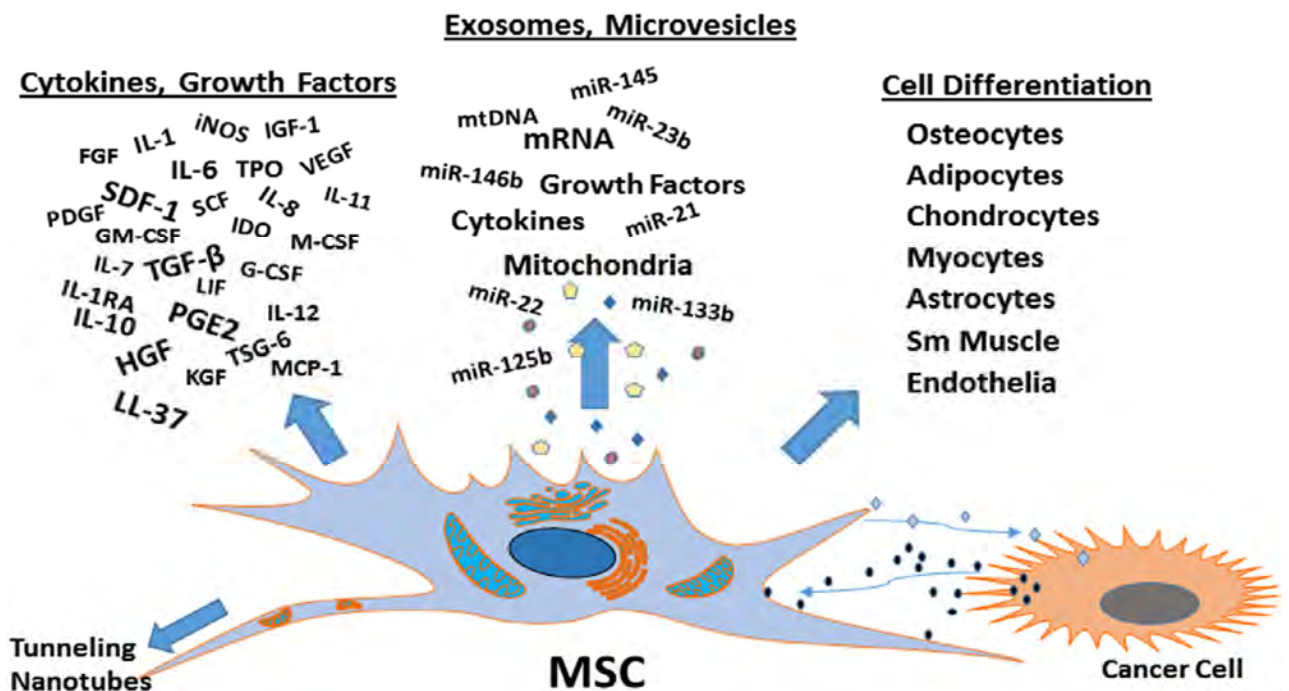
## 間質幹細胞的免疫調節特性



Trends In Pharmacological Sciences

Trends in Pharmacological Sciences 41(9): 653 – 664 (2020)

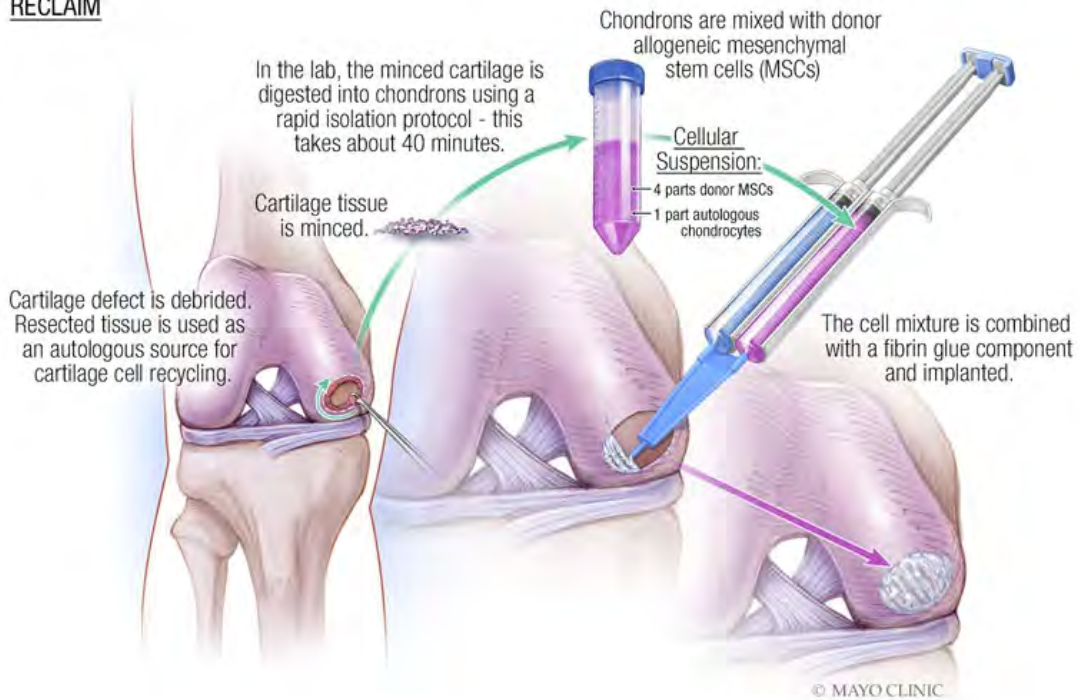
## 間質幹細胞的旁分泌與外泌體



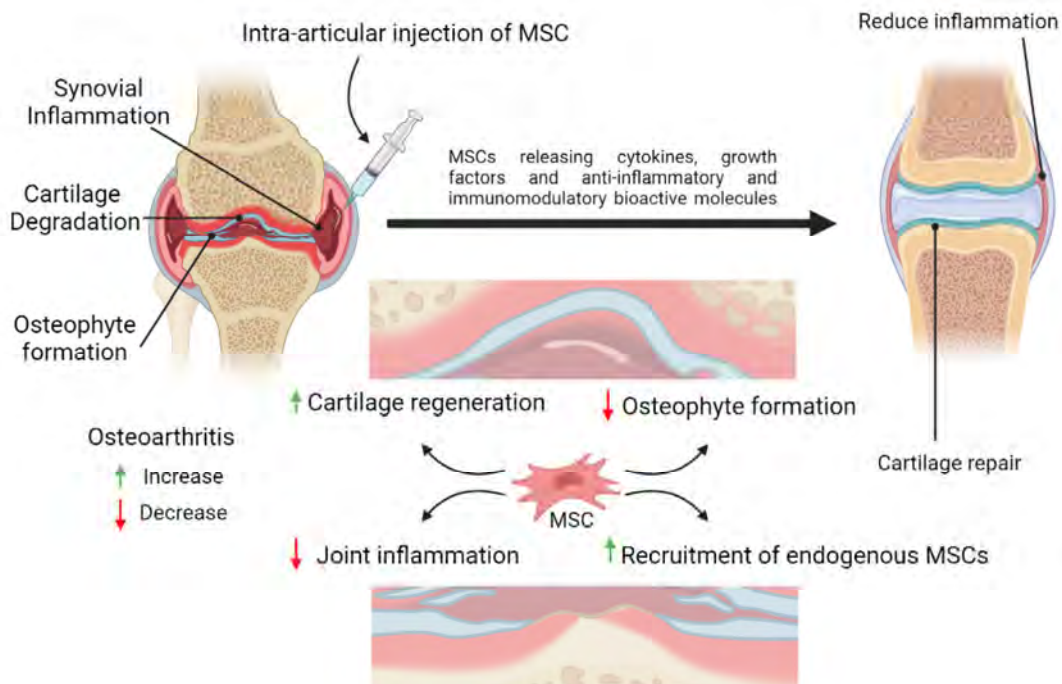
STEM CELLS 35(4):851-858 (2017)

# 間質幹細胞修復關節軟骨

## RECLAIM

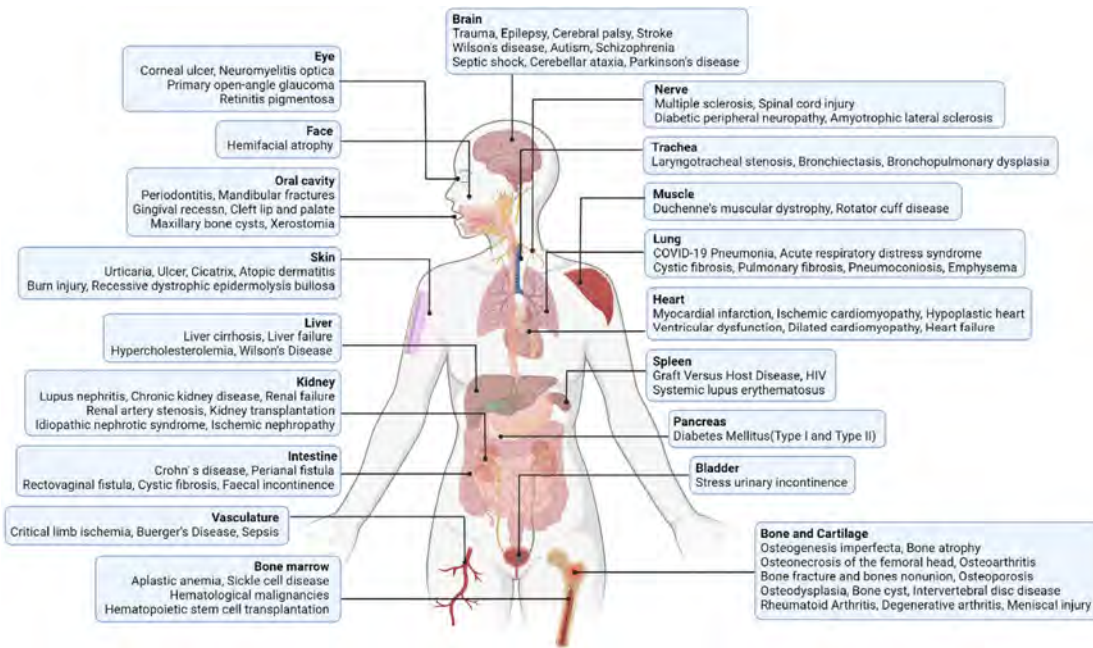


# 間質幹細胞治療關節炎

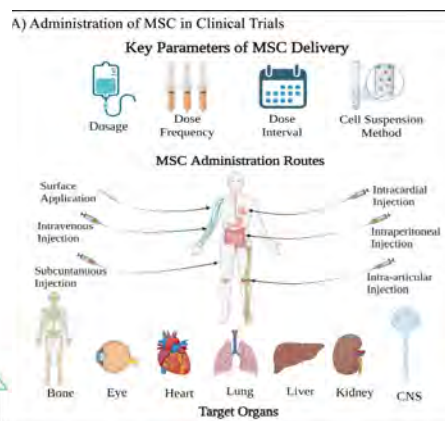
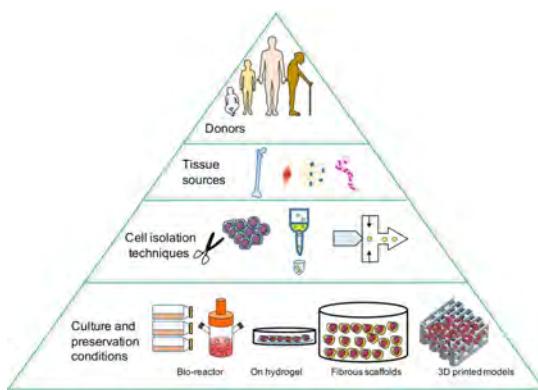


# 間質幹細胞的臨床應用潛能

- MSC-based clinical trials are mainly applied to the diseases associated with inflammation, wound healing, infection, as well as degeneration in diverse organs



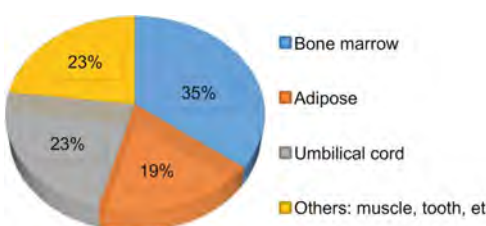
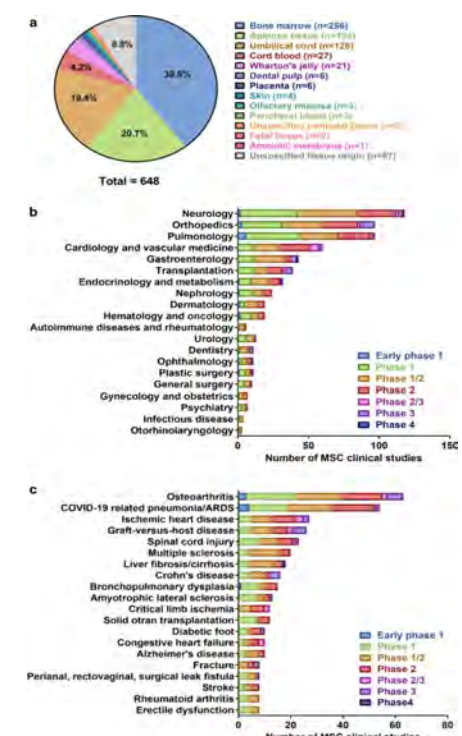
# 間質幹細胞的臨床應用潛能



**B) Clinical trials classified by medical specialty-disease category**

Medical specialty	Number of CT
Musculoskeletal	212
Neurology	163
Pneumology	117
Immunology	73
Cardiology	63
Hepatology	50
Endocrinology	48
Reproduction	33
Oncology	27
Dermatology	30
Nephrology	27
Gastroenterology	26
Ophthalmology	19
Anal Disorders	14
Aging	7
Urology	6
Hematology	6
Psychiatry	4
HIV	2
Other	91
Total	1014

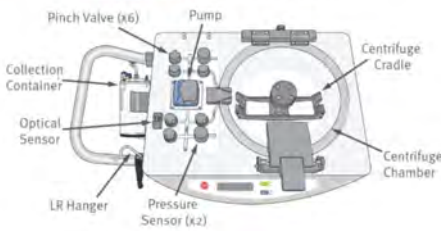
\*COVID-19 (65)



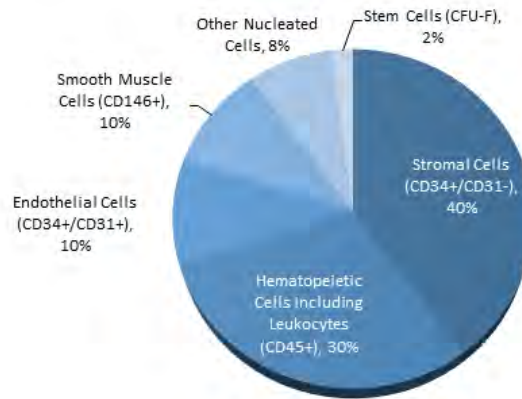
## 脂肪間質幹細胞的產業應用



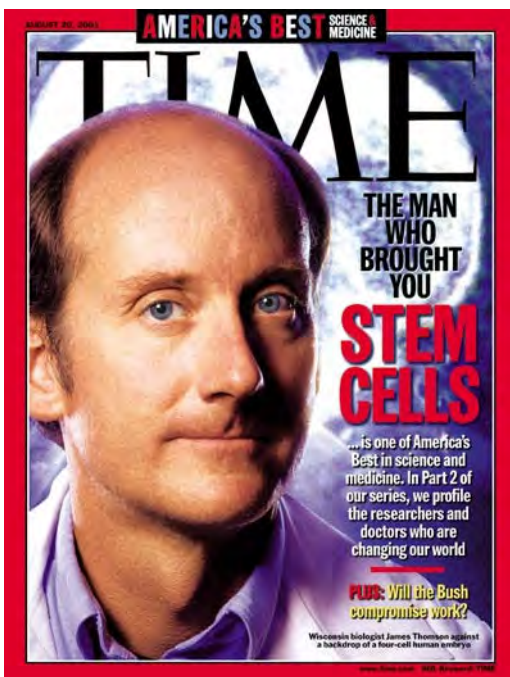
celution<sup>OP</sup> DEVICE OVERVIEW



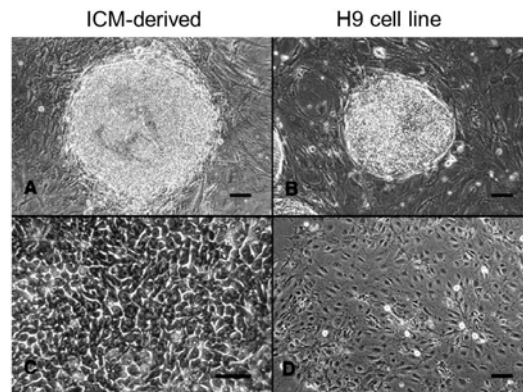
- ✓ Cytori is developing cell therapies that harness the unique attributes of living cells that are present in an adult human patient's own adipose (fat) tissue, also known as Adipose-Derived Regenerative Cells (ADRCs).
- ✓ Cytori Cell Therapy is the collective name given to the fresh, heterogeneous population of ADRCs prepared with the proprietary Celution<sup>®</sup> System platform technology and administered to a patient for a specific disease or medical condition, all within a single day:



## 人類胚胎幹細胞株的建立



Derivation of embryonic stem cells from human embryos



Differentiating cells

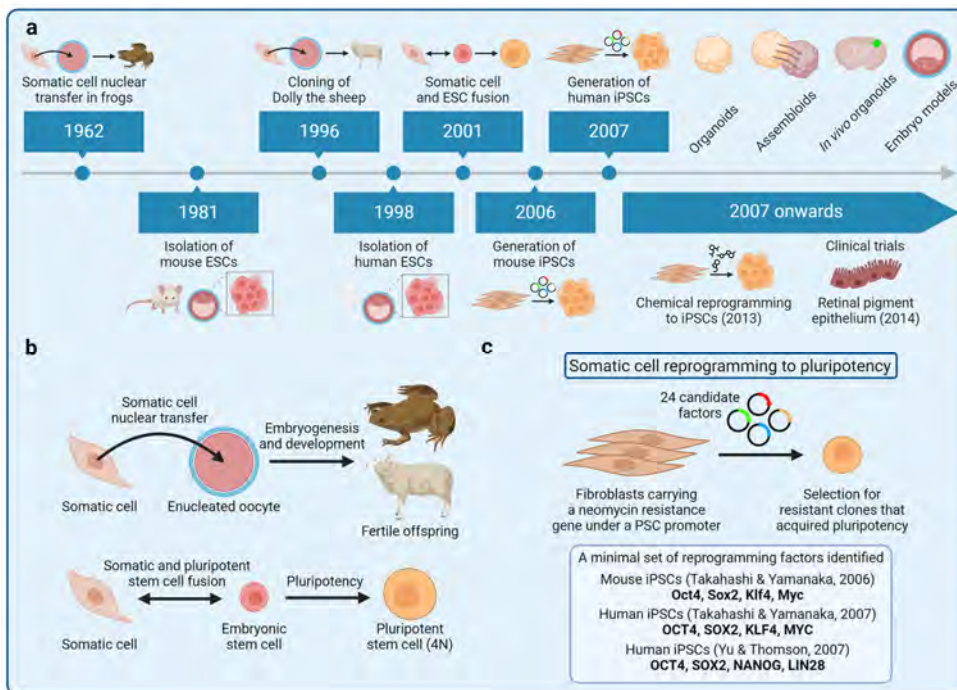
Thomson, et al., Science, 1998

# 胚胎多潛能幹細胞/誘導多潛能幹細胞的研發歷程



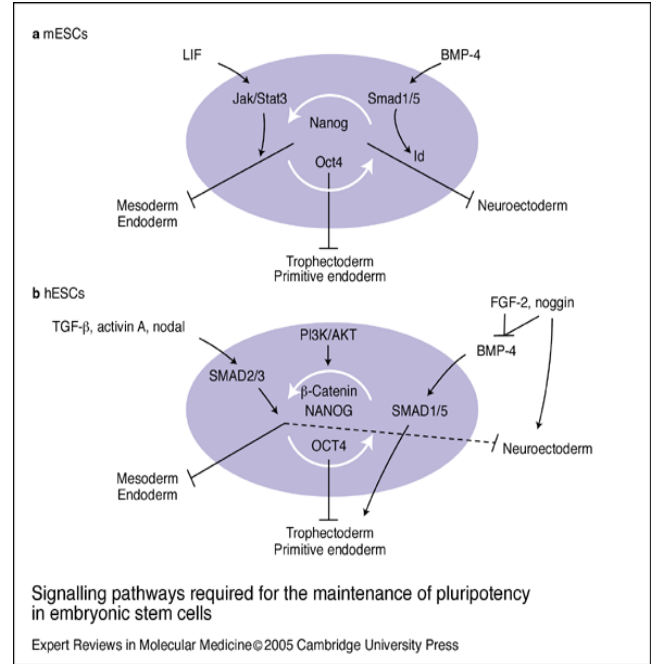
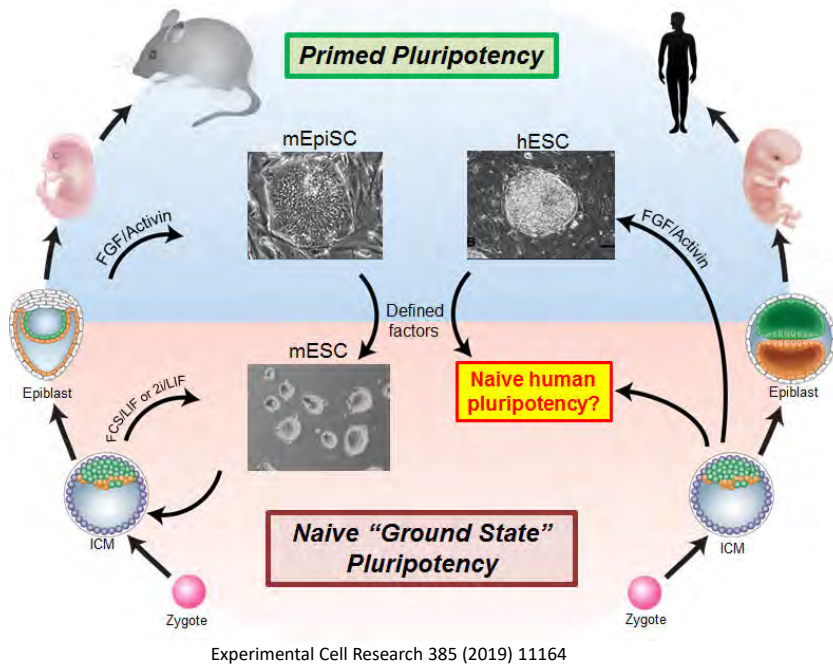
Front. Cell Dev. Biol., 2015

# 胚胎多潛能幹細胞/誘導多潛能幹細胞的研發歷程

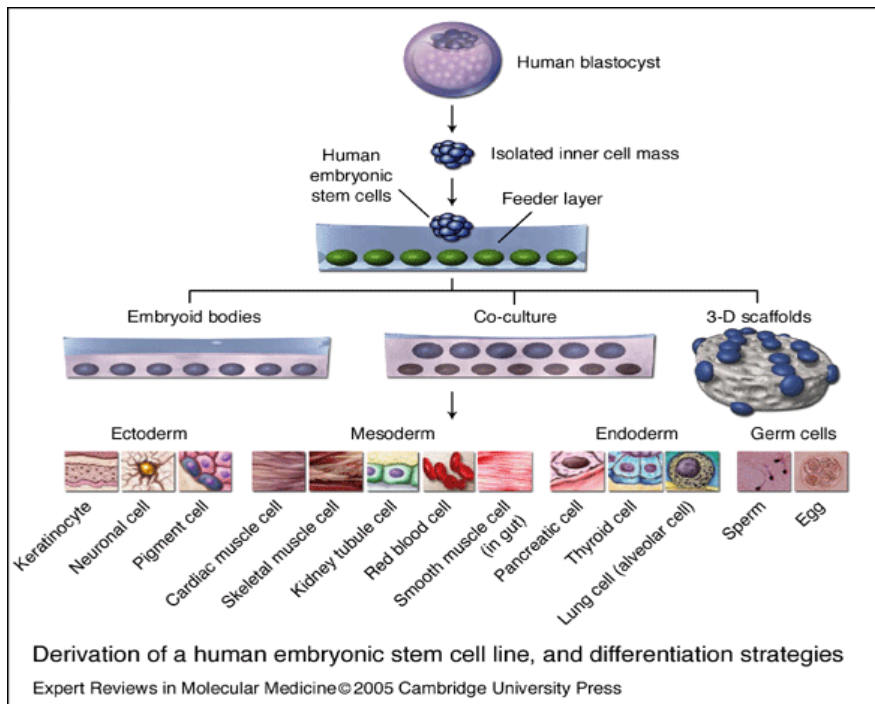


Sig Transduct Target Ther 9, 112 (2024)

# 人類胚胎幹細胞株的建立



# 人類胚胎幹細胞株的多潛能分化特性

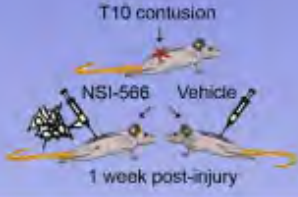


# 人類胚胎幹細胞株的臨床應用

**Preclinical Studies**


Differentiation of grafted NSI-566:  
- neurons  
- oligodendrocytes  
- astrocytes

Migration of grafted NSI-566 cells





**Intraspinal Injections**

Phase 1 clinical trial  
n=4 adult subjects  
Thoracic ASIA A spinal cord injury  
1-2 years after injury  
6 bilateral injections  
2 x 10<sup>6</sup> cells/injection via stereotactic floating cannula



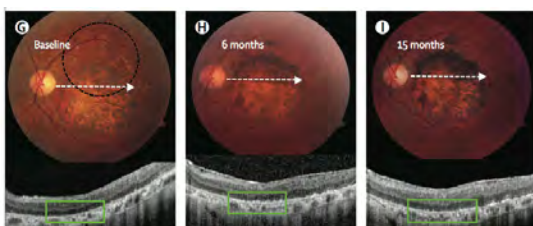
**Clinical Follow-up**

Presence of antibodies  
ISNCSCI Exam  
Neurophysiology  
Imaging  
Quality of Life  
Pain

Indication	Severe heart failure	Type 1 diabetes	Spinal cord injury	Parkinson disease
Product	hESC-cardiac progenitors	Encapsulated hESC-pancreatic endoderm cells (VC-01)	hESC-oligodendrocyte progenitors (GRN-OPC1)	PSC-dopaminergic neurons (still in development)
Trial #	NCT02057900	NCT02239354	NCT01217008	NA
Trial phase	1	1/2	1	NA
Trial status	Recruiting	Recruiting	Completed	NA
Sponsor	Assistance Publique-Hospitiaux de Paris	ViaCyte	Asterias Biotherapeutics (acquired Geron's technology)	Several potential sponsors (e.g., NY Stem Cell Foundation, Kyoto University, and others)
Location	France	USA	USA	TBD
Indication			Spinal cord injury	
Product			hESC-oligodendrocyte progenitors (AST-OPC1)	
Trial #			NCT02302157	
Phase			1/2	
Status			Recruiting	
Sponsor			Asterias Biotherapeutics	
Location			USA	

# 人類胚胎幹細胞株應用於視網膜疾病的治療的臨床試驗



- Ocata Therapeutics Inc. (formerly Advanced Cell Technology) has been running a clinical program since 2011 with a Phase I/II open-label, multicenter, nonrandomized, prospective study to determine the safety and potential efficacy of subretinal RPE cells spontaneously produced from hESCs (MA09-hRPE).
- Patients with GA in dry AMD (NCT01344993) and Stargardt's disease (NCT01345006) had pars plana vitrectomies and were subretinally transplanted with 50,000 to 200,000 hESC-derived RPE cells.
- Nine eyes in patients with GA and nine eyes in patients with Stargardt's disease were transplanted and followed for a median of 22 months. No treated eyes developed abnormal tissue proliferation, teratoma formation, rejection or inflammation. Of treated eyes, 72 percent had patches of increasing subretinal pigmentation consistent with viable, transplanted RPE.

Product (name)	Trial #	Indication	Trial phase	Status	Sponsor	Location
hESC-RPE (MA09-RPE)	NCT01344993	Dry AMD	1/2	Completed	AIRM	USA
hESC-RPE (MA09-RPE)	NCT01345006	Stargardt disease	1/2	Completed	AIRM	USA
hESC-RPE (MA09-RPE)	NCT01469832	Stargardt disease	1/2	Completed	AIRM	UK
hESC-RPE (MA09-RPE)	NCT01674829	Dry AMD	1/2	Unknown	CHA Biotech (licensed from AIRM)	Korea
hESC-RPE (MA09-RPE)	NCT01625559	Stargardt disease	1	Unknown	CHA Biotech (licensed from AIRM)	Korea
hESC-RPE (MA09-RPE)	NCT02563782	Dry AMD	2	Not recruiting	AIRM	USA
hESC-RPE (CPBP-RPE1)	NCT02590692	Dry AMD	1/2	Recruiting	Regenerative Patch Technologies	USA
hESC-RPE (Opregen)	NCT02286089	Dry AMD	1/2	Recruiting	Cell Cure Neurosciences	Israel
hESC-RPE (PF-05206388)	NCT01691261	Wet AMD	1	Not recruiting	Pfizer	UK
hESC-RPE	NCT02749734	AMD & Stargardt	1	Recruiting	Southwest Hospital Chongqing	China
hESC-RPE	NCT02755428	Dry AMD	0	Recruiting	Chinese Academy of Sciences	China
iPSC-RPE	NA	Wet AMD	1	On hold	RIKEN	Japan

Information extracted from <http://clinicaltrials.gov>

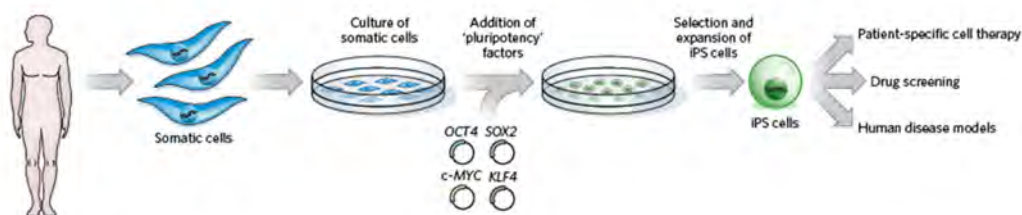
## 人類胚胎幹細胞株應用的倫理爭議

- At present most human embryonic stem cells can only be obtained by destroying live human embryos at the blastocyst stage
- They proliferate rapidly and are extremely versatile, but there is scant scientific evidence that embryonic stem cells will form normal tissues in a culture dish
- Embryonic stem cells are difficult to develop into a stable cell line. It spontaneously accumulate genetic abnormalities in embryonic-stem cell cultures
- Embryonic stem cells are prone to uncontrollable growth and tumor formation when placed in animals



## 誘導式多潛能幹細胞技術

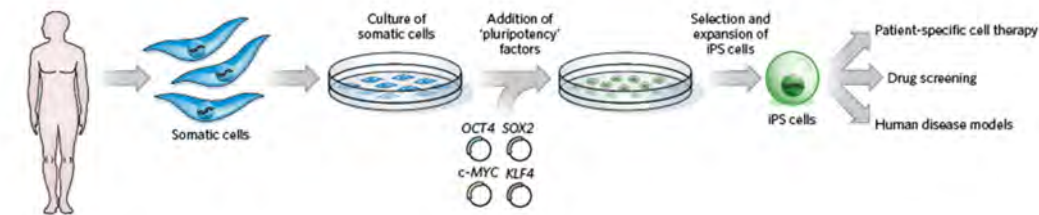
人體珍貴的幹細胞有辦法可以不必從胚胎取得嗎？



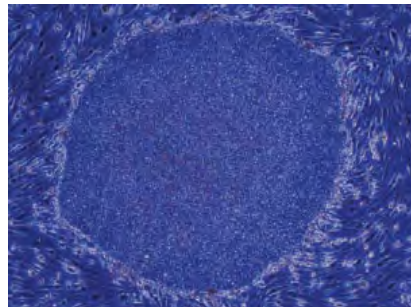
- 日本京都大學教授山中伸彌從早期胚胎表現的基因中找出四個主要的基因成功地將將既有的成年小鼠皮膚細胞，創造出如幹細胞一樣有分化成器官組織的功能，稱為誘導式萬能幹細胞(induced pluripotent stem cells)
- 這項發現一方面解決了利用胚胎進行幹細胞研究的道德爭議，另一方面也使得幹細胞研究的來源更不受限。

# 誘導式多潛能幹細胞技術

➤ Reprogramming somatic cells to pluripotent ESC-like cells using define factors (induced pluripotent stem cells, iPSCs)



Shinya Yamanaka  
Kyoto University



2009 Albert Lasker Basic Medical Research Award  
2012 The Nobel Prize in Physiology or Medicine

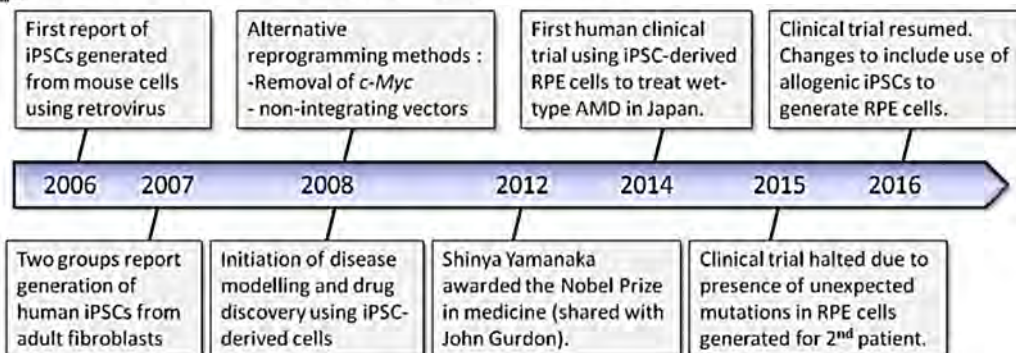
## 人類誘導式多潛能幹細胞技術的建立與應用

### Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi<sup>1,2</sup> and Shinya Yamanaka<sup>1,2,3,4</sup>

Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts

Masasa Nakagawa<sup>1,2</sup>, Michiru Koyanagi<sup>1,2</sup>, Koji Tanabe<sup>1</sup>, Kazumichi Takahashi<sup>1</sup>, Tomoko Ichihata<sup>1,2</sup>, Takashi Aoi<sup>1</sup>, Kazuhiko Okita<sup>1</sup>, Yui Mochizuki<sup>1</sup>, Naohiko Takizawa<sup>1</sup> & Shinya Yamanaka<sup>1,2,3,4</sup>



Debbie King Cell Culture Dish 2016

### Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi<sup>1</sup>, Koji Tanabe<sup>1</sup>, Masashi Ohnuki<sup>1</sup>, Megumi Nishita<sup>1,2</sup>, Tomoko Ichihata<sup>1,2</sup>, Nichiko Tomoda<sup>1</sup> and Shinya Yamanaka<sup>1,2,3,4</sup>



Treatment of Sickle Cell Anemia Mouse Model with iPSC Cells Generated from Autologous Skin  
Jacob Hanna, et al.  
*Science* 318, 1920 (2007);  
DOI: 10.1126/science.1152092



### Scienceexpress Report

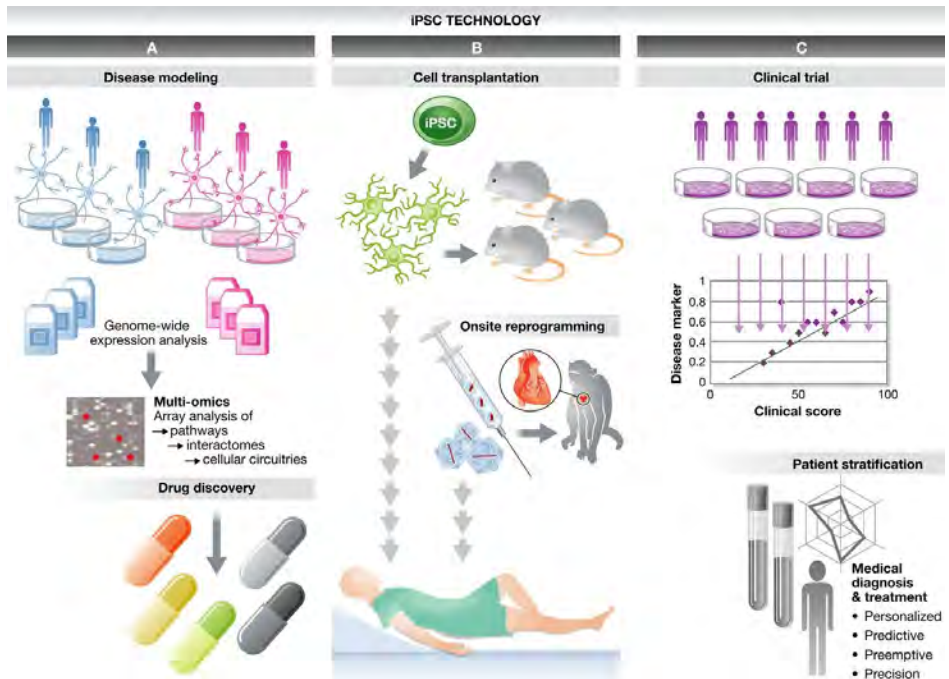
#### Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

Juziyang Yu<sup>1,2,3</sup>, Masaru A. Vodyanil<sup>1</sup>, Kim Sumagi-Otto<sup>1,2</sup>, Jevica Antovijevic-Bowyer<sup>1,2</sup>, Jennifer L. Finze<sup>1</sup>, Shalini Tiwari<sup>1</sup>, Jeff Nie<sup>1</sup>, Guleria A. Joodatani<sup>1</sup>, Victor Ruzini<sup>1</sup>, Ron Stewart<sup>1</sup>, Igen I. Shkvan<sup>1,4</sup>, James A. Thomson<sup>1,2,3,5</sup>



Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons  
John T. Dimos, et al.  
*Science* 321, 1218 (2008);  
DOI: 10.1126/science.1158799

# 人類誘導式多潛能幹細胞的應用潛能



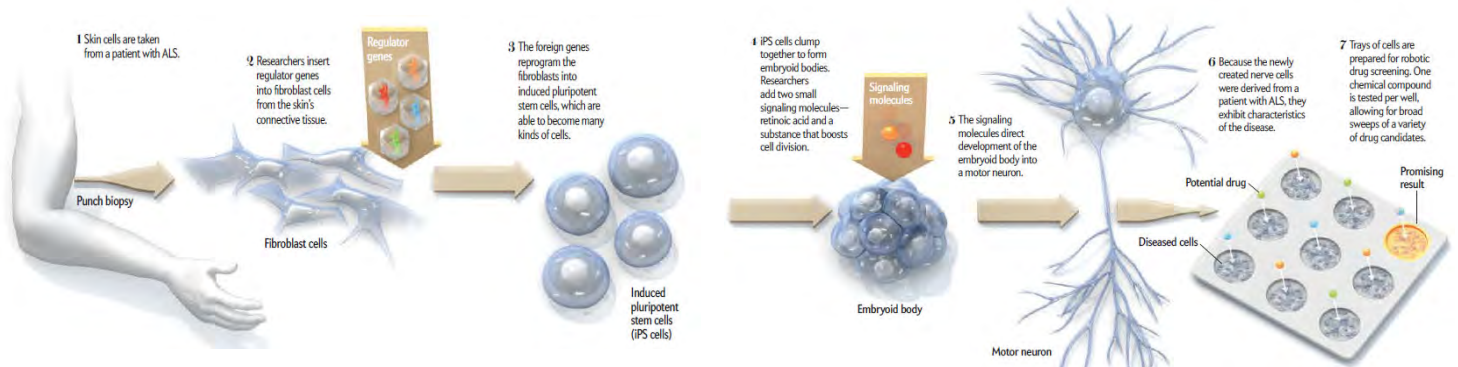
Haruhisa Inoue et al. EMBO J. 2014;embj.201387098

# 漸凍人病患特異誘導式多潛能幹細胞的建立與應用



## Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons

John T. Dimos, et al.  
 Science 321, 1218 (2008);  
 DOI: 10.1126/science.1158799



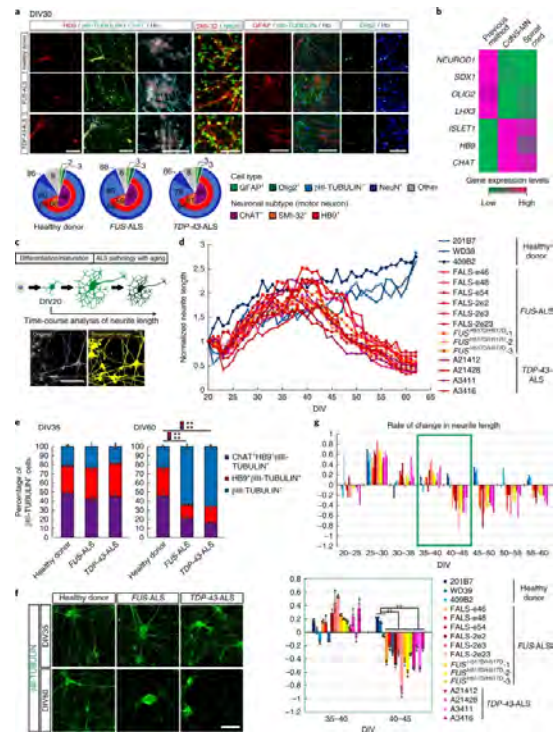
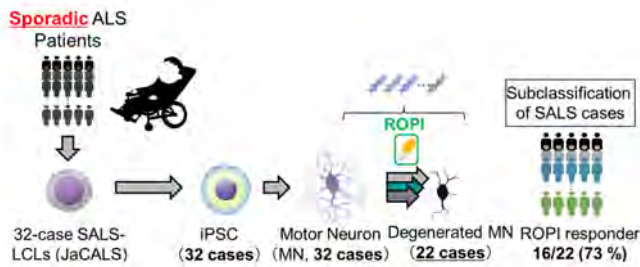
# 漸凍人病患特異誘導式多潛能幹細胞應用疾病研究

**nature medicine** ARTICLES  
<https://doi.org/10.1038/s41591-018-0140-5>

## Modeling sporadic ALS in iPSC-derived motor neurons identifies a potential therapeutic agent

Koki Fujimori<sup>1</sup>, Mitsuru Ishikawa<sup>1</sup>, Asako Otomo<sup>2,3,4</sup>, Naoki Atsuta<sup>5</sup>, Ryoichi Nakamura<sup>5</sup>, Tetsuya Akiyama<sup>6</sup>, Shinji Hadano<sup>2,7</sup>, Masashi Aoki<sup>8</sup>, Hideyuki Saya<sup>9,10</sup>, Gen Sobue<sup>11</sup> and Hideyuki Okano<sup>11\*</sup>

**Abstract** Amyotrophic lateral sclerosis (ALS) is a heterogeneous motor neuron disease for which no effective treatment is available, despite decades of research into SOD1-mutant familial ALS (FALS). The majority of ALS patients have no familial history, making the modeling of sporadic ALS (SALS) essential to the development of ALS therapeutics. However, as mutations underlying ALS pathogenesis have not yet been identified, it remains difficult to establish useful models of SALS. Using induced pluripotent stem cell (iPSC) technology to generate stem and differentiated cells retaining the patients' full genetic information, we have established a large number of in vitro cellular models of SALS. These models showed phenotypic differences in their pattern of neuronal degeneration, types of abnormal protein aggregates, cell death mechanisms, and onset and progression of these phenotypes in vitro among cases. We therefore developed a system for case clustering capable of subdividing these heterogeneous SALS models by their in vitro characteristics. We further evaluated multiple-phenotype rescue of these subclassified SALS models using agents selected from non-SOD1 FALS models, and identified ropinirole as a potential therapeutic candidate. Integration of the datasets acquired in this study permitted the visualization of molecular pathologies shared across a wide range of SALS models.



# 漸凍人病患特異誘導式多潛能幹細胞應用疾病研究

**CellPress** OPEN ACCESS **Cell Stem Cell**

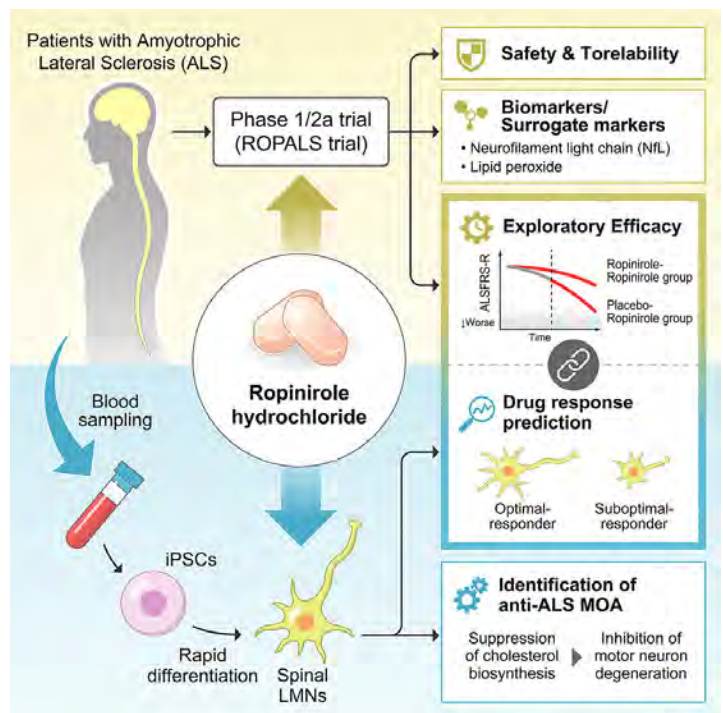
## Clinical and Translational Report Phase 1/2a clinical trial in ALS with ropinirole, a drug candidate identified by iPSC drug discovery

Satoru Morimoto<sup>1,2,13</sup>, Shinichi Takahashi<sup>1,2,13,14</sup>, Daisuke Ito<sup>1,2</sup>, Yuguaku Daito<sup>1</sup>, Kensuke Okada<sup>2</sup>, Chris Kato<sup>1</sup>, Shingo Nakamura<sup>1</sup>, Fumiko Ozawa<sup>1</sup>, Chai Muh Chyi<sup>1,5</sup>, Ayumi Nishiyama<sup>1</sup>, Naoki Suzuki<sup>1</sup>, Koki Fujimori<sup>1</sup>, Toshio Kondo<sup>1</sup>, Masaki Takao<sup>1,6</sup>, Miwa Hira<sup>1</sup>, Yasuaki Kabre<sup>1</sup>, Makoto Sumatsu<sup>1</sup>, Masahiro Jirakki<sup>1</sup>, Masashi Aoki<sup>1</sup>, Yuto Fujiki<sup>1</sup>, Yasunori Sato<sup>1,7</sup>, Norihito Suzuki<sup>2</sup>, Jin Nakahara<sup>1</sup>, The Pooled Resource Open-Access ALS Clinical Trials Consortium, and Hideyuki Okano<sup>1,14\*</sup>

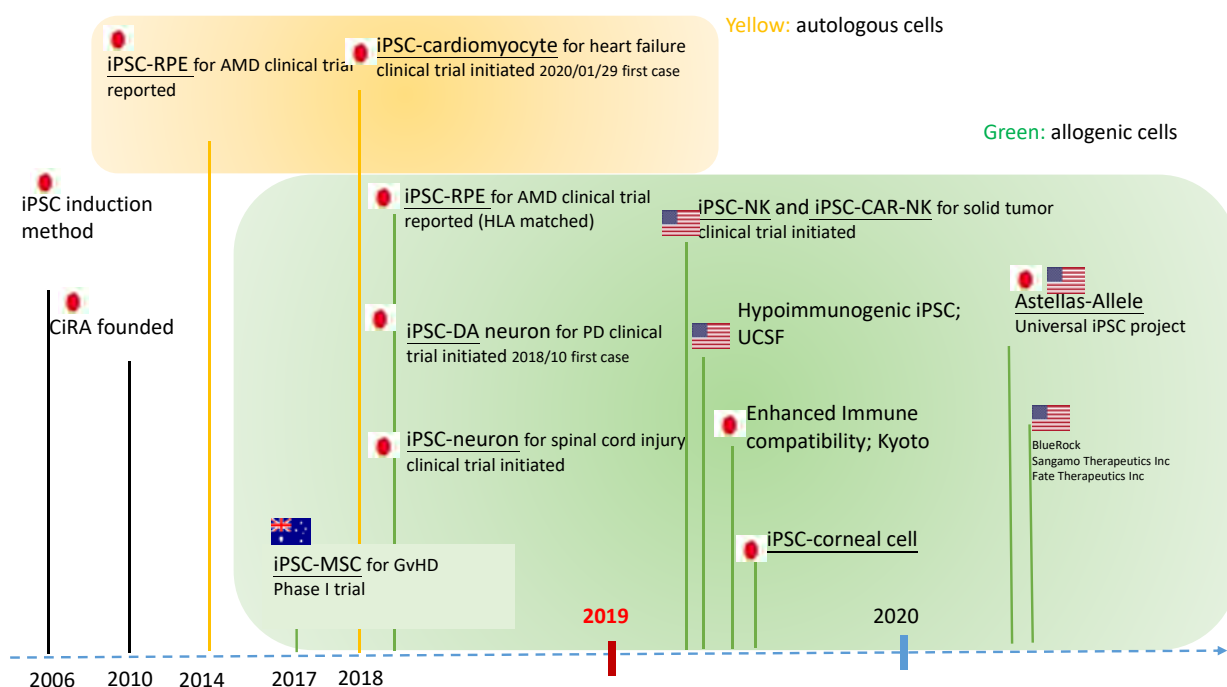
<sup>1</sup>Department of Physiology, Keio University School of Medicine, Tokyo 160-8582, Japan  
<sup>2</sup>Department of Neurology, Keio University School of Medicine, Tokyo 160-8582, Japan  
<sup>3</sup>Department of Neurology and Stroke, Satama Medical University International Medical Center, Satama 350-1298, Japan  
<sup>4</sup>Keio University Global Research Institute, Tokyo 108-8345, Japan  
<sup>5</sup>Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Miyagi 980-8575, Japan  
<sup>6</sup>Research Center of Neurology, ONO Pharmaceutical Co., Ltd., Osaka 541-8504, Japan  
<sup>7</sup>Department of Clinical Laboratory, National Center of Neurology and Psychiatry (NCNP), Tokyo 167-0031, Japan  
<sup>8</sup>Department of Neurology, Mihara Memorial Hospital, Ise-shi, Gunma 372-0008, Japan  
<sup>9</sup>Department of Biochemistry, Keio University School of Medicine, Tokyo 160-8582, Japan  
<sup>10</sup>Department of Radiology, Keio University School of Medicine, Tokyo 160-8582, Japan  
<sup>11</sup>Keio University Hospital Clinical and Translational Research Center, Tokyo 160-8582, Japan  
<sup>12</sup>Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo 160-8582, Japan  
<sup>13</sup>These authors contributed equally  
<sup>14</sup>Lead contact  
 \*Correspondence: [hiddakari@keio.jp](mailto:hiddakari@keio.jp)  
<https://doi.org/10.1016/j.stem.2023.04.017>

### SUMMARY

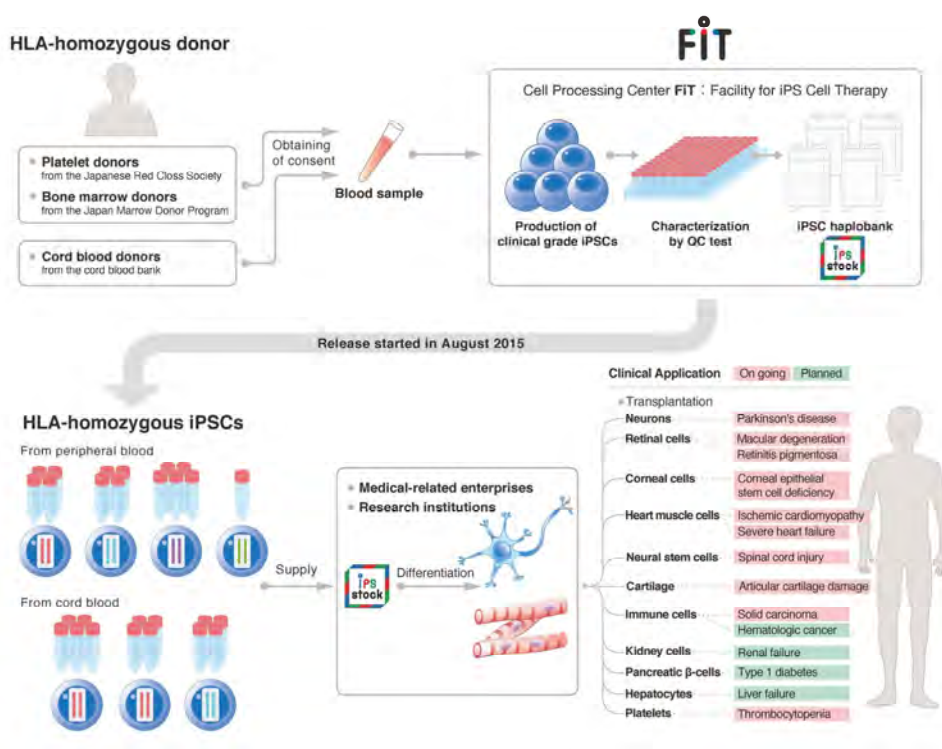
iPSC-based drug discovery led to a phase 1/2a trial of ropinirole in ALS. 20 participants with sporadic ALS received ropinirole or placebo for 24 weeks in the double-blind period to evaluate safety, tolerability, and therapeutic effects. Adverse events were similar in both groups. During the double-blind period, muscle strength and daily activity were maintained, but a decline in the ALSFRS-R, which assesses the functional status of ALS patients, was not different from that in the placebo group. However, in the open-label extension period, the ropinirole group showed significant suppression of ALSFRS-R decline and an additional 27.9 weeks of disease-progression-free survival. iPSC-derived motor neurons from participants showed dopamine D2 receptor expression and a potential involvement of the SREBP2-cholesterol pathway in therapeutic effects. Lipid peroxide represents a clinical surrogate marker to assess disease progression and drug efficacy. Limitations include small sample sizes and high attrition rates in the open-label extension period, requiring further validation.



# 人類誘導式多潛能幹細胞的臨床應用潛能



# 人類誘導式多潛能幹細胞的臨床應用潛能



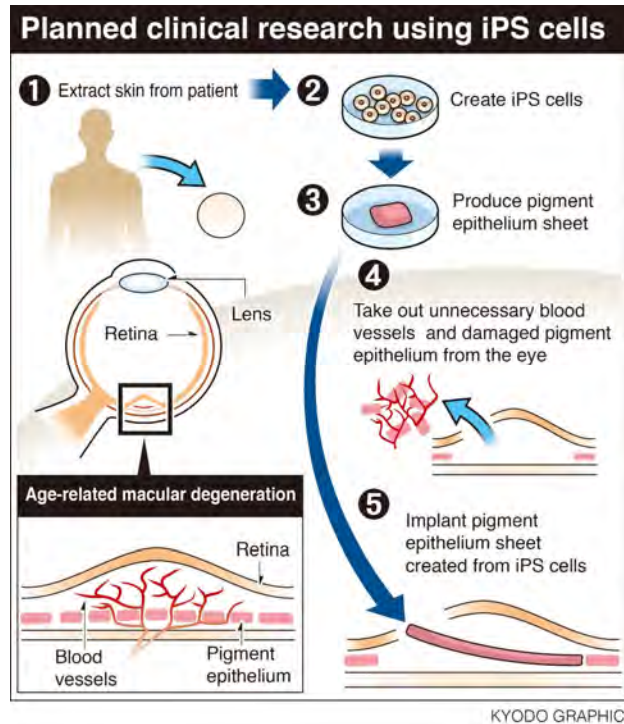
# 人類誘導式多潛能幹細胞治療視網膜病變

ノーベル賞山中教授の悲願  
iPS細胞を「人体移植」  
「世界初」の手術

IPS細胞から作製した細胞が  
人の体に移植される「世界初の手術」

**Transplantation of  
iPS cell-derived  
retinal pigment epithelial cells**

Center for Developmental Biology, RIKEN  
Laboratory for Retinal Regeneration  
Kobe City Medical Center General Hospital  
Ophthalmology department  
Institute of Biomedical Research and Innovation Hospital  
Ophthalmology, Section  
Center for iPS cell Research & Application, Kyoto University  
Visiting Professor  
**Masayo Takahashi MD, PhD**



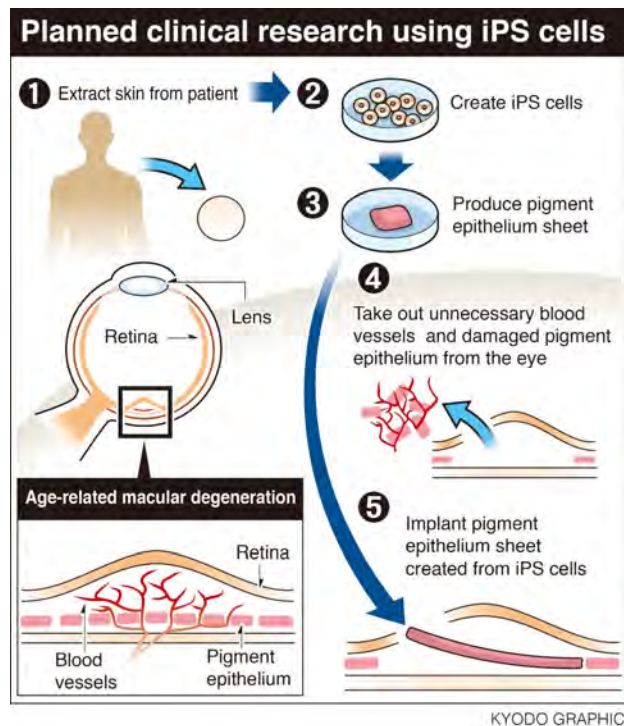
# 人類誘導式多潛能幹細胞治療視網膜病變

ノーベル賞山中教授の悲願  
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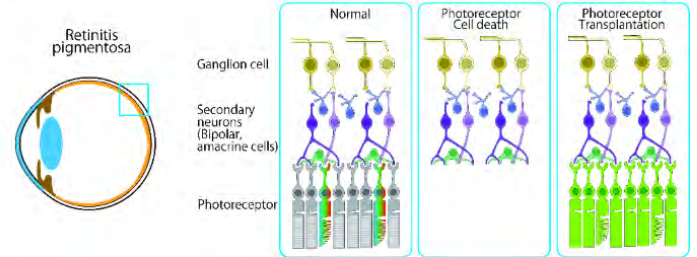
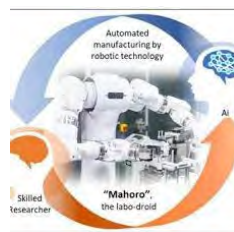
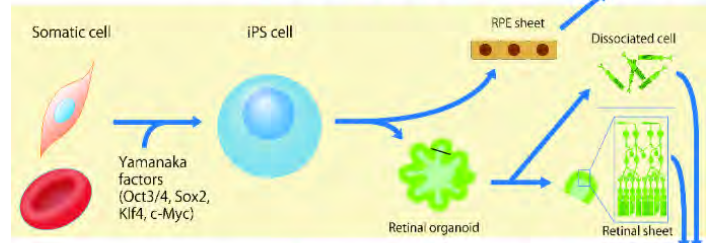
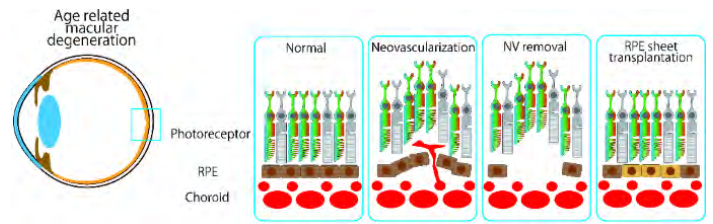
IPS細胞から作製した細胞が  
人の体に移植される「世界初の手術」

**Transplantation of  
iPS cell-derived  
retinal pigment epithelial cells**

Center for Developmental Biology, RIKEN  
Laboratory for Retinal Regeneration  
Kobe City Medical Center General Hospital  
Ophthalmology department  
Institute of Biomedical Research and Innovation Hospital  
Ophthalmology, Section  
Center for iPS cell Research & Application, Kyoto University  
Visiting Professor  
**Masayo Takahashi MD, PhD**



# 人類誘導式多潛能幹細胞治療視網膜病變

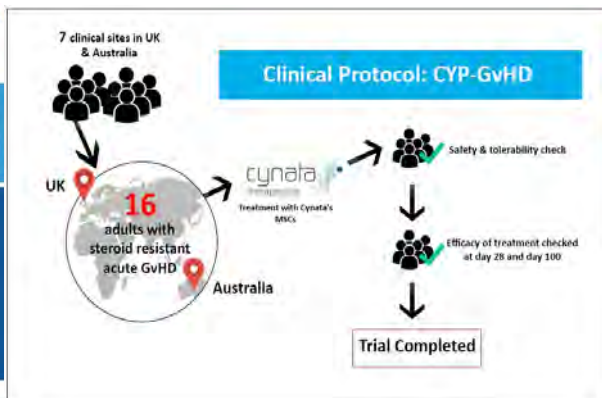
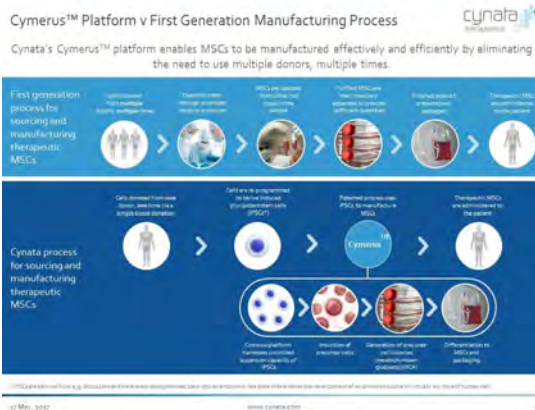


# 誘導性多潛能幹細胞產製間質幹細胞 (治療移植物對抗宿主疾病)

**06** World first for allogeneic iPSC-derived cell therapy: Cynata gains clinical trial approval from UK regulatory authority

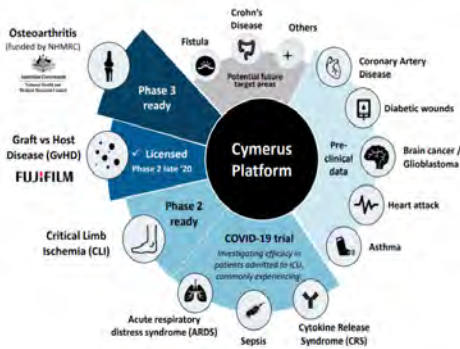
Oct 6 October 2016

Melbourne, Australia; 19 September 2016: Australian stem cell and regenerative medicine company, Cynata Therapeutics Limited (ASX: CYP) has received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) to proceed with its Phase 1 clinical trial of CYP-001 in patients with steroid-resistant graft-versus-host disease (GvHD). CYP-001 is Cynata's lead Cymerus™ mesenchymal stem cell (MSC) product.



# 誘導性多潛能幹細胞產製間質幹細胞 (治療免疫疾病)

Cynata's Cymerus platform has potential applications across a wide range of diseases



Product	Indications	Dose (delivery)	Status	Next milestone	Notes
CYP - 001	acute Graft vs host disease/ organ transplantation	Intravenous	Phase 2 planning	Bypass Phase 2 - Excellent phase 1 results facilitate Cynata progressing directly to phase 2/3 clinical trials in multiple other indications	Phase 1 results published in prestigious journal, Nature Medicine. Overall response = 87%. Survival rate ≥ 87%. US\$2m payment on Phase 2 completion.
CYP - 001	Respiratory failure (inc ARDS)	Intravenous	24 pt Phase 2 underway (open for enrolment).	First patient enrolled 24/05/2021. Beginning Q3FY22 headline results from study should be available.	Trial is currently open for enrolment. Cynata to execute strategy to accelerate recruitment.
CYP - 002	Critical limb ischaemia	Intramuscular	Phase 2 ready	Currently on hold	Encouraging efficacy signals in preclinical study.
CYP - 004	Knee Osteoarthritis	Intra-articular	440pt Phase 3 underway - funded by a NHMRC grant	11 Nov - Patient enrolment opened and trial commenced, seeking 440 patients.	Funded by a NHMRC grant (no cash contribution from Cynata) and sponsored by University of Sydney.
TBD	Diabetic foot ulcers	MSC-seeded silicon dressing	Phase 1/2 planning	Cynata expects trial to commence in 2H CY21	Worldwide exclusive licence agreement to Tekyte's wound dressing technology for use in diabetic foot ulcer clinical trial.

Source: Cynata Therapeutics.

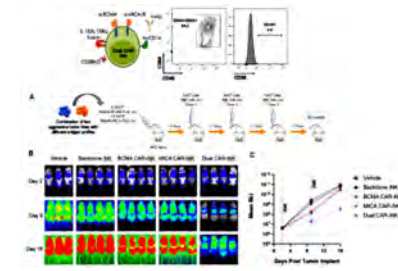
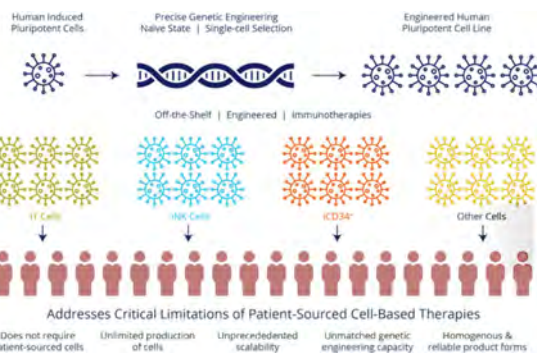
# 誘導性多潛能幹細胞產製自然殺手細胞治療癌症

## First Off-the-Shelf Immunotherapy Clinical Trial Launched

NEWS | (biopharma/news) © Apr 11, 2019 | Original story by Yadira Galindo, UC San Diego Health (https://www.technologynetworks.com/tn/go/iv/view-source-318100)



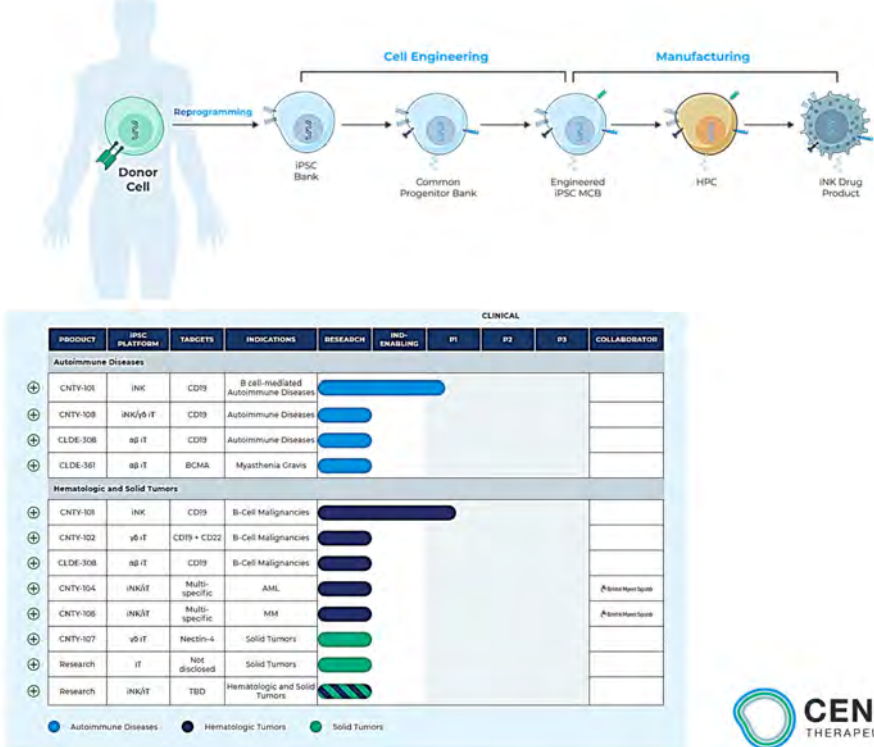
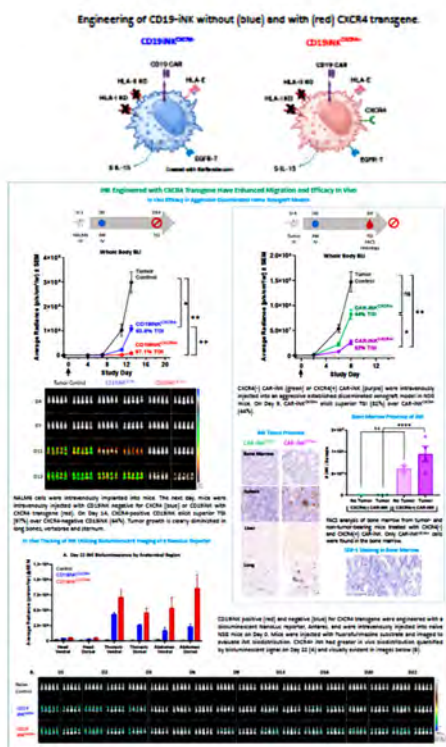
Sandip Patel, MD, and Dan Kaufman, MD, PhD, of UC San Diego School of Medicine enjoy a light-hearted moment before Derek Ruff receives the first treatment for cancer of a human-induced pluripotent stem cell (iPSC)-derived cell therapy called FT500. Image credit: UC San Diego Health



PROGRAM (CELL TYPE)	INDICATION	CAR TARGET(S)	RESEARCH	PRECLINICAL	PHASE 1	PARTNER
<b>CAR T-CELL PRODUCT CANDIDATES</b>						
FT819	Systemic Lupus Erythematosus	CD19	Progressing	Progressing	Progressing	
FT825	Solid Tumors	HER2	Progressing	Progressing	Progressing	ONO
Undisclosed	Solid Tumors	Undisclosed	Progressing	Progressing	Progressing	
FT836	Multiple Tumor Types	MICAB	Progressing	Progressing	Progressing	
Next gen iTs	Multiple Therapeutic Areas	Undisclosed	Progressing	Progressing	Progressing	
<b>CAR NK CELL PRODUCT CANDIDATES</b>						
FT522	B-cell Lymphoma	CD19, 4-1BB	Progressing	Progressing	Progressing	
FT522	Autoimmunity	CD19, 4-1BB	Progressing	Progressing	Progressing	
Next gen iNKs	Multiple Therapeutic Areas	Undisclosed	Progressing	Progressing	Progressing	



# 誘導性多潛能幹細胞產製自然殺手細胞治療癌症



## 幹細胞治療的風險

Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient

Hinette Amaniglo<sup>1,2</sup>, Abraham Hirschberg<sup>3</sup>, Bernd W. Scheithauer<sup>4</sup>, Yoram Cohen<sup>5</sup>, Ron Loewenthal<sup>7</sup>, Luba Trahtenberg<sup>8</sup>, Nurit Paz<sup>1</sup>, Maya Koren-Michowitz<sup>2</sup>, Dalia Waldman<sup>9</sup>, Leonor Leider-Trejo<sup>7</sup>, Amos Toren<sup>10</sup>, Shlomi Constantini<sup>6</sup>, Gidon Rechavi<sup>1,6\*</sup>



**Table 2 Overview of risk factors and risks associated with stem cell-based therapy**

	Risk factors or hazards	Identified risks	
Intrinsic factors	- Origin of cells (e.g. autologous vs. allogeneic, diseased vs. healthy donor/tissue)	- Rejection of cells	
Cell characteristics	- Differentiation status	- Disease susceptibility	
	- Tumorigenic potential	- Unwanted biological effect (e.g. in vivo differentiation in unwanted cell type)	
	- Proliferation capacity	- Toxicity	
	- Life span	- neoplasm formation (benign or malignant)	
	- Long term viability		
	- Excretion patterns (e.g. growth factors, cytokines, chemokines)		
Extrinsic factors	- Lack of donor history	- Disease transmission	
Manufacturing and handling	- Starting and raw materials	- Reactivation of latent viruses	
	- Plasma derived materials	- Cell line contamination (e.g. with unwanted cells, growth media components, chemical)	
	- Contamination by adventitious agents (viral/bacterial/mycoplasma/fungi, prions, parasites)	- Mixup of autologous patient material	
	- Cell handling procedures (e.g. procurement)	- neoplasm formation (benign or malignant)	
	- Culture duration	- Culture duration	
	- Tumorigenic potential (e.g. culture induced transformation, incomplete removal of undifferentiated cells)		
	- Non cellular components		
	- Pooling of allogeneic cell populations		
	- Conservation (e.g. cryopreservation)		
	- Storage conditions (e.g. failure of traceability, human material labeling)		
	- Transport conditions		
	Clinical characteristics	- Therapeutic use (i.e. homologous or non-homologous)	- Undesired immune response (e.g. GVHD)
		- Indication	- Unintended physiological and anatomical consequences (e.g. arrhythmia)
		- Administration route	- Engraftment at unwanted location
- Initiation of immune responses		- Toxicity	
- Use of immune suppressives		- Lack of efficacy	
- Exposure duration		- neoplasm formation (benign or malignant)	
- Underlying disease			
- Irreversibility of the treatment			

- 排斥
- 非預期效應
- 細胞毒性
- 致癌風險
- 疾病傳播
- 病毒活化
- 細胞污染
- 致癌風險
- 非預期免疫反應
- 移植在不正確的位置
- 細胞毒性
- 致癌風先

## 幹細胞治療非萬靈丹

- Stem cells have the potential to treat certain diseases and conditions, particularly those involving tissue damage or degeneration. **However, they are not effective for all diseases, and their application is limited by current scientific understanding and technological capabilities.**
- Stem cell treatments require extensive research and clinical trials to ensure they are safe and effective.

## 幹細胞治療的參考文獻

