細胞治療與再生醫學之現況與國際趨勢

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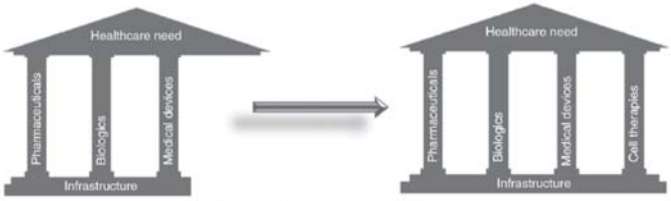
Taipei Medical University

Executive Director
TACT /TSSCR

2018 TSQA

細胞治療與健康照護
老化與醫療未滿足疾病



Therapeutic pillars of health care
(Figure adapted and edited from Mason et al'11)

Table 1. Therapeutics and core competencies for the industries that make up the four pillars of healthcare.

	Therapeutic product	Core technologies	Industry
小分子藥	Small molecule drug	Chemistry	Pharmaceutical Industry
蛋白質藥	Macromolecule drug	Genetic engineering Monoclonal antibody	Biotech
醫療器材	Medical device	Physics Engineering	Medical Device Industry
細胞治療	Cell therapy	Cells Tissue engineering	Cell Therapy Industry

Reg Med (2011) 6(3):265-272

細胞治療
未來新核心醫療領域

PERSPECTIVE

INNOVATION

Cell-Based Therapeutics: The Next Pillar of Medicine

www.ScienceTranslationalMedicine.org 3 April 2013 Vol 5 Issue 179 179ps7

Michael A. Fischbach,[1,2*] Jeffrey A. Bluestone,[3] Wendell A. Lim[1,4,5*]

Two decades ago, the pharmaceutical industry—long dominated by small-molecule drugs—was revolutionized by the the advent of biologics. Today, biomedicine sits on the cusp of a new revolution: the use of microbial and human cells as versatile therapeutic engines. Here, we discuss the promise of this "third pillar" of therapeutics in the context of current scientific, regulatory, economic, and perceptual challenges. History suggests that the advent of cellular medicines will require the development of a foundational cellular engineering science that provides a systematic framework for safely and predictably altering and regulating cellular behaviors.

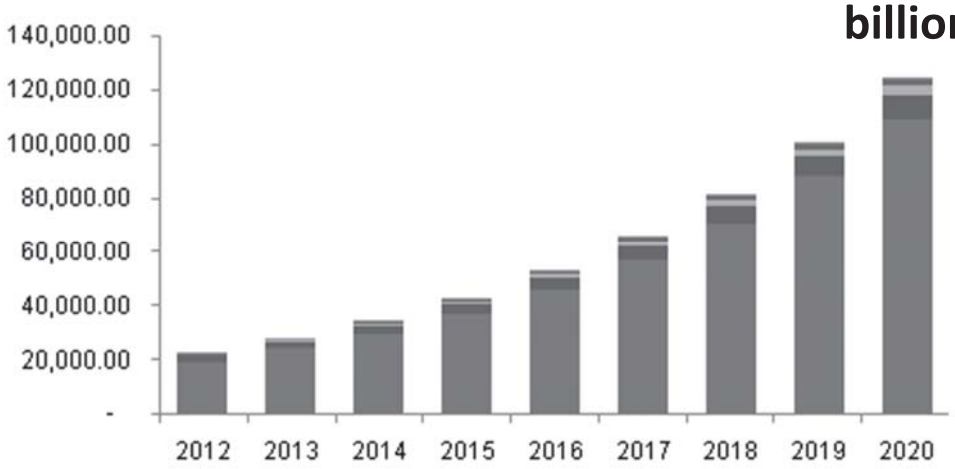
免疫細胞
癌症治療

幹細胞
再生醫學

Rita YH Huang

Adult Cell Dominates the Rising Stem Cell Market

120 USD billions



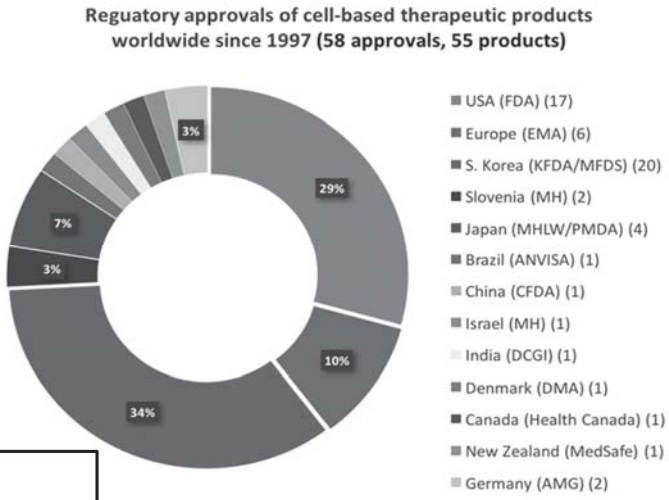
North America stem cells market, by product, 2012-2020 (USD Million)

- Very Small Embryonic Like Stem Cells
- Natural Rosette Cells
- Induced Pluripotent Stem Cells
- Human Embryonic Stem Cells
- Adult Stem Cells

Pluripotent stem cells:
Tumor risk
Epigenetic aberration
Ethical concern

2015 Grant Review Research Report ID: 978-1-68038-130-6

台灣目前尚無細胞產品核准上市
2018 最快進度為臨床試驗二期 (查驗登記)



3 products were approved by more than one jurisdiction.
(Provenge, Prochymal, and MACI).

http://celltrials.info/2017/04/07/marketed-approveds

Rita YH Huang

Future Hope for Human ESC Clinical Trials

ACT (Robert Lanza)
Macular degeneration ESC clinical trials are ongoing.

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

2012

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.

Lancet 2012; 379:713-20
Published Online
January 23, 2012

Stem Cell Reports
Article

ISSCR

OPEN ACCESS

Treatment of Macular Degeneration Using Embryonic Stem Cell-Derived Retinal Pigment Epithelium: Preliminary Results in Asian Patients

Won Kyung Song, Kyung-Mi Park, Hyun-Ju Kim, Jae Ho Lee, Jinjung Choi, So Young Chong, Sung Han Shim, Lucian V. Del Priore, and Robert Lanza

2015 Asia MD Patients

SUMMARY

Embryonic stem cells hold great promise for various diseases because of their unlimited capacity for self-renewal and ability to differentiate into any cell type in the body. However, despite over 3 decades of research, there have been no reports on the safety and potential efficacy of pluripotent stem cell progeny in Asian patients with any disease. Here, we report the safety and tolerability of subretinal transplantation of human embryonic-stem-cell (hESC)-derived retinal pigment epithelium in four Asian patients: two with dry age-related macular degeneration and two with Stargardt macular dystrophy. They were followed for 1 year. There was no evidence of adverse proliferation, tumorigenicity, ectopic tissue formation, or other serious safety issues related to the transplanted cells. Visual acuity improved 9–19 letters in three patients and remained stable (±1 letter) in one patient. The results confirmed that hESC-derived cells could serve as a potentially safe new source for regenerative medicine.

Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies

Steven D Schwartz, Carl D Regillo, Byron L Lam, Dean Eliott, Philip J Rosenfeld, Nirvel Z Gregori, Jean-Pierre Hubschman, Janet L Davis, Gad Heilwell, Marc Spirn, Joseph Maguire, Roger Gay, Jane Bateman, Rosaleen M Ostrick, Debra Morris, Matthew Vincent, Eddy Anglade, Lucian V Del Priore, Robert Lanza

2015 AMD

Summary

Background Since they were first derived more than three decades ago, embryonic stem cells have been proposed as a source of replacement cells in regenerative medicine, but their plasticity and unlimited capacity for self-renewal raises concerns about their safety, including tumour formation ability, potential immune rejection, and the risk of differentiating into unwanted cell types. We report the medium-term to long-term safety of cells derived from human embryonic stem cells (hESC) transplanted into patients.

Lancet 2015; 385: 509-16
Published Online
October 15, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61376-3

nature biotechnology

2018 AMD

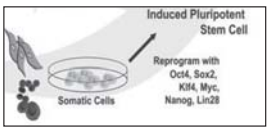
Phase 1 clinical study of an embryonic stem cell–derived retinal pigment epithelium patch in age-related macular degeneration

Lyndon da Cruz, Kate Fynes, Odysseas Georgiadis, Julie Kerby, Yvonne H Luo, Ahmad Ahmado, Amanda Vernon, Julie T Daniels, Britta Nommiste, Shazeen M Hasan, Sakina B Gooljar, Amanda-Jayne F Carr, Anthony Vugler, Conor M Ramsden, Magda Bictash, Mike Fenster, Juliette Steer, Tricia Harbinson, Anna Wilbrey, Adnan Tufail, Gang Feng, Mark Whitlock, Anthony G Robson, Graham E Holder, Mandeep S Sagoo, Peter T Loudon, Paul Whiting & Peter J Coffey

Age-related macular degeneration (AMD) remains a major cause of blindness, with dysfunction and loss of retinal pigment epithelium (RPE) central to disease progression. We engineered an RPE patch comprising a fully differentiated, human embryonic stem cell (hESC)–derived RPE monolayer on a coated, synthetic basement membrane. We delivered the patch, using a purpose-designed microsurgical tool, into the subretinal space of one eye in each of two patients with severe exudative AMD. Primary endpoints were incidence and severity of adverse events and proportion of subjects with improved best-corrected visual acuity of 15 letters or more. We report successful delivery and survival of the RPE patch by biomicroscopy and optical coherence tomography, and a visual acuity gain of 29 and 21 letters in the two patients, respectively, over 12 months. Only local immunosuppression was used long-term. We also present the preclinical surgical, cell safety and tumorigenicity studies leading to trial approval. This work supports the feasibility and safety of hESC-RPE patch transplantation as a regenerative strategy for AMD.

iPSC CT for Age-Related Macular Degeneration in Japan
Autograft and Allograft (2012-2018)

2012 Nobel Prize Winner



NATIONAL / SCIENCE & HEALTH

Japanese government panel OKs world's first clinical research using iPS cells **2013 Clinical research**

KYODO

A government panel Wednesday approved the world's first clinical research using human induced pluripotent stem (iPS) cells, which can grow into any type of human body tissue, officials said.

JUN 27, 2013
ARTICLE HISTORY

NATURE | NEWS

Japan stem-cell trial stirs envy

Researchers elsewhere can't wait to test iPS cells in humans.

Sara Reardon & David Cyranoski **2014 CT-I**

16 September 2014

The first patient, a 70-year-old woman, **was treated with iPSCs and was reportedly in good health**.

New Scientist

63

DAILY NEWS 21 July 2015

2015 CT-II halted

Mutation alert halts stem-cell trial to cure blindness

A pioneering stem-cell trial has been halted after genetic mutations were discovered in the cells of the second trial participant. One of the mutations may carry a remote risk of cancer.

Good stem cell news as Takahashi IPS Cell Trial to Resume

Posted on **June 7, 2016**

2016

CT Resumed

Some good news today as the pioneering induced pluripotent stem (IPS) cell trial led by Dr. Masayo Takahashi will resume.

February 7, 2017

Green light for launch of clinical research using donor iPS cells

On February 6, a press conference was held in Kobe to announce the launch of a clinical research project aimed at establishing an induced pluripotent stem cell (iPSC)-based treatment for wet-type age-related macular degeneration, which has been reviewed and assessed by all required Japanese regulatory bodies.

The project leaders at the press conference

The project will be led by Yasuo Kurimoto and Masayo Takahashi of Kobe City Medical Center General Hospital, and Osaka University's Graduate School of Medicine/ Faculty of Medicine, and will be conduc
Biolog
Applic
for Retinal Regeneration at RIKEN CDB.

2017 iPSC Allograft CT

Tuesday in Kobe. | KYODO

NATIONAL / SCIENCE & HEALTH

First serious adverse reaction to iPS-derived retinal cell transplant reported

KYODO

KOBE – A patient who underwent transplant surgery using retinal cells derived from so-called iPS cells from another person has suffered a swollen retina, the team that carried out the world's first clinical trial of the procedure said Tuesday.

It is the first time a patient has developed a serious adverse reaction during the clinical research to assess the feasibility of using the artificially derived induced pluripotent stem cells, said the researchers from Kobe City Medical Center General Hospital and the government-backed Riken institute.

JAN 11, 2018
ARTICLE HISTORY
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PHOTOS
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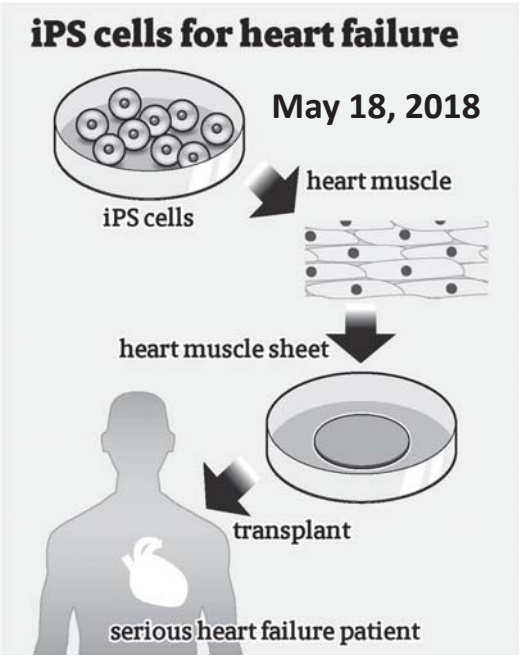
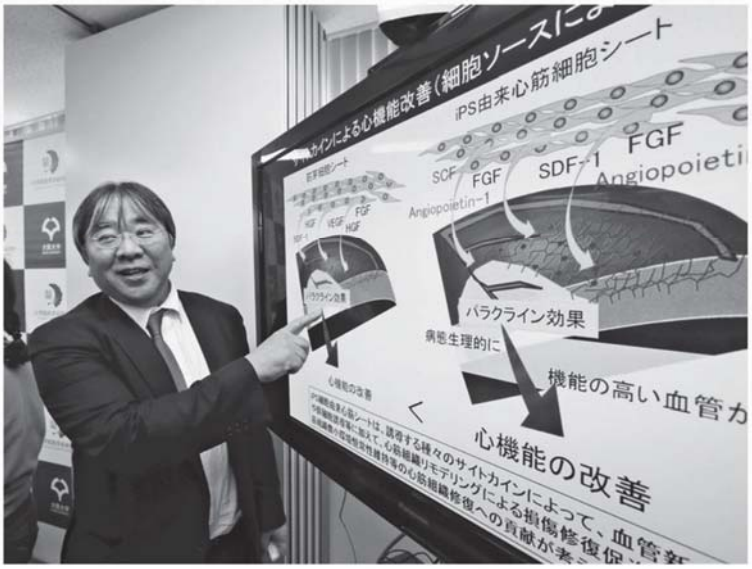
2018 iPSC Allograft SAE

iPSC-Derived Cell Sheet for Cardiovascular Disease



Panel OK's stem cells trial for heart disease treatment

Like 66 Share ツイート G+ B! 0 CLIP Share



Prof. Yoshiki Sawa, Osaka University

EDITORIAL · 29 MAY 2018 **May 29, 2018**

Stem-cell tests must show success

Nature. 2018 May;557(7707):611-612

Japan needs to demonstrate that a promising therapy for damaged hearts works as claimed.

At a press conference in Tokyo, cardiac surgeon Yoshiki Sawa announces plans to use tissue derived from induced pluripotent stem cells to treat heart disease.

CLINICAL RESEARCH

Reprogrammed stem cells approved to mend hearts

Japanese study is only the second application of induced pluripotent stem cells in people.

Prof. Yoshiki Sawa
Osaka University

iPSCs for Parkinson's Diseases

Launch of Jun Takahashi IPS Cell Trial For Parkinson's Disease

July 30, 2018

July 30, 2018 admin IPS cells, japan stem cells 6

Share this:

A much-anticipated i
Parkinson's Disease
Takahashi.

The news broke on Y
appropriately sober
exciting trial as well,

Parkinson's Disease
brain so it is a partic
can be readily used t

Here are some key d
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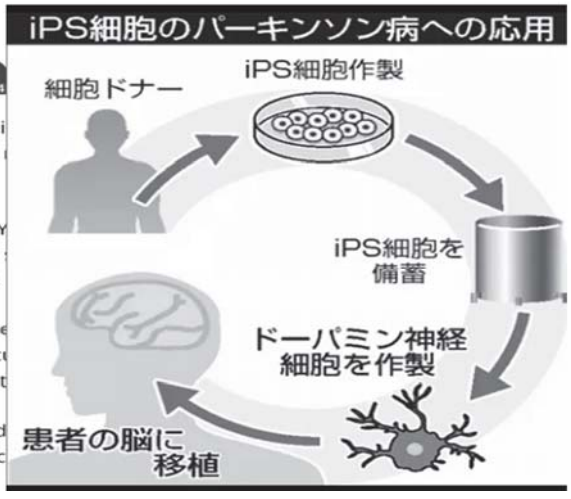
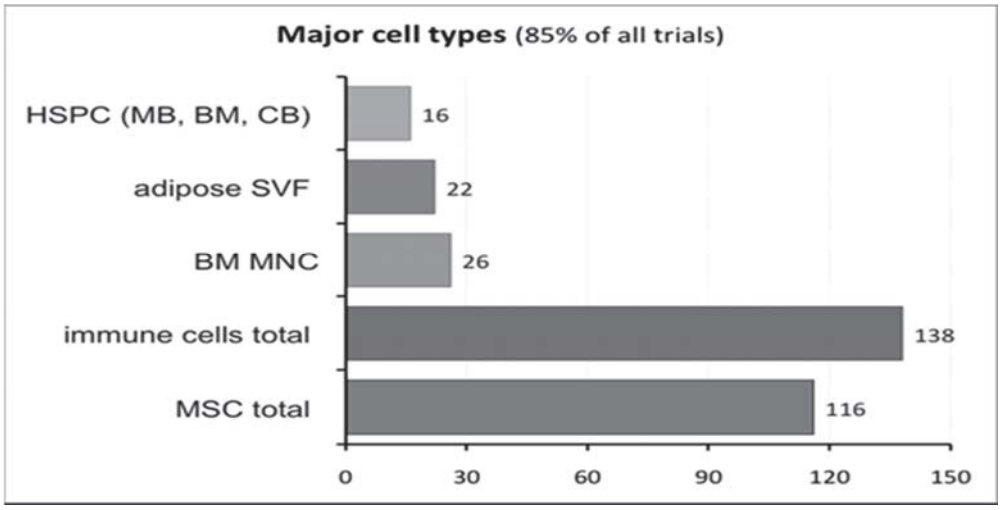


Prof. Jun Takahashi

間質(幹)細胞與免疫細胞
全球臨床試驗主要細胞種類



Rita YH Huang

Cell Type for Cell Therapy

Adult cells: Adult stem cells, Adult cells, and Immune cells

Product Insights

1. **Adult cells dominate the industry.**
2. **Safety is the first priority, then the Efficacy.**
3. **Key technologies are cell production, acquisition, cryopreservation, sub-culture, and expansion.**
4. **Low contamination probability during expansion and sub-culture, and better acceptance by human body is very important.**

Failure of Adult Allo-MSC (Osiris) Phase III aGvHD CT in Japan

PRESS RELEASE
May 17, 2012, 4:36 p.m. EDT

World's First Approved Stem Cell Drug; Osiris Receives Marketing Clearance from Health Canada for Prochymal

Historic decision offers hope to children suffering from life-threatening GvHD

Osiris THERAPEUTICS, INC.

2012 BMMSC Allograft/aGVHD
New Zealand/Canada

There are no statistical difference between prochymal and placebo on the primary endpoints for either the steroid-refractory (35% vs 30% n=260) or the first line (45% vs 46% n=192) GvHD Phase III clinical Trials.

Mesoblast Ltd mesoblast the adult stem cell company

We Need Quality Control for Cell Products

Industrial Allo-MSC Product Failure Analysis

Stem Cell Assays
Promoting Rigorous Reproducible Research on Stem Cells

Failure of mesenchymal stem cells in GVHD – is devil in the cell prep?

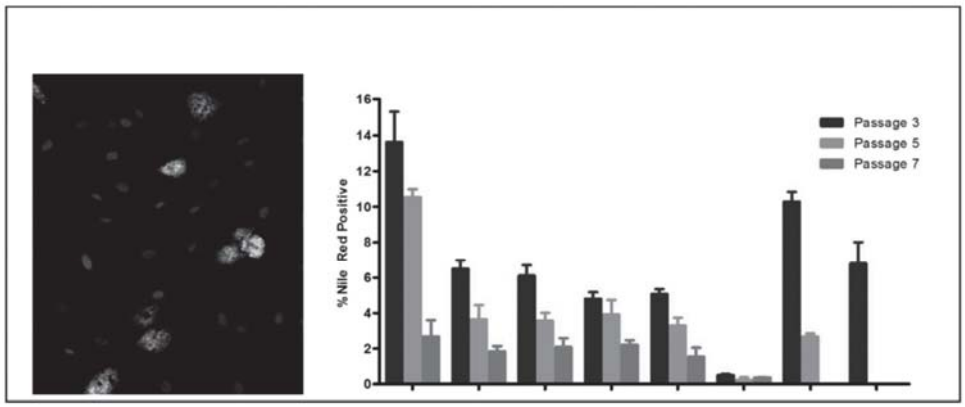
by ALEXEY BERSENEV on JANUARY 26, 2013 · 2 COMMENTS
in CELL PRODUCT, MESENCHYMAL

As we all know, Phase III clinical trial, sponsored by Osiris Therapeutics and assessed efficacy of mesenchymal stem cells (MSC) (product "Prochymal") for treatment of Graft-Versus-Host-Disease (GVHD) failed more than 3 years ago. **The possible reasons of failure were not analyzed and discussed publicly by community**. Contrary to Osiris trial, similar "academic trials" in Europe were quite successful in Phase II. Recently, for the first time, Jacques Galipeau presents **Prochymal failure analysis, based on discrepancy between MSC-based product characteriazation and preparation for US industry-sponsored trial versus European academic trials**.

- **Culture expansion**
- **Serum culture condition (Niche)**
- **Epigenetic (Aging-related)**
- **Reprogramming and senescence**
- **Tissue/Donor variance**
- **Cryopreservation**
- **Immunogenicity: HLA**

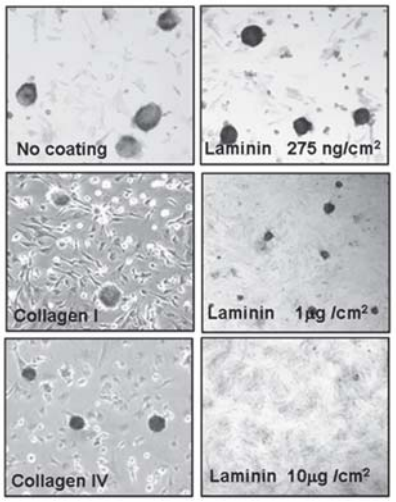
細胞治療產品--非最小操作 (細胞不同來源與培養CMC)

人類細胞治療產品臨床試驗及查驗登記審查基準



Left panel: Shows mesenchymal stem cells (MSCs) after treatment to induce fat cell formation. Blue indicates cell nuclei; green indicates the presence of fat revealed by a dye called Nile Red. Right panel: MSCs treated to make fat cells were counted to determine how many—using different donors—were successful in transforming and how long the cultures lasted (a concept known as passage). Passage refers to the duration of cell culture. The graph shows that the number of MSCs that can turn into fat decreases over time. Also, the ability of MSCs to turn into fat is different between MSCs from different donors.

MSC Heterogeneity, Steven R. Bauer, 2015 ISCT

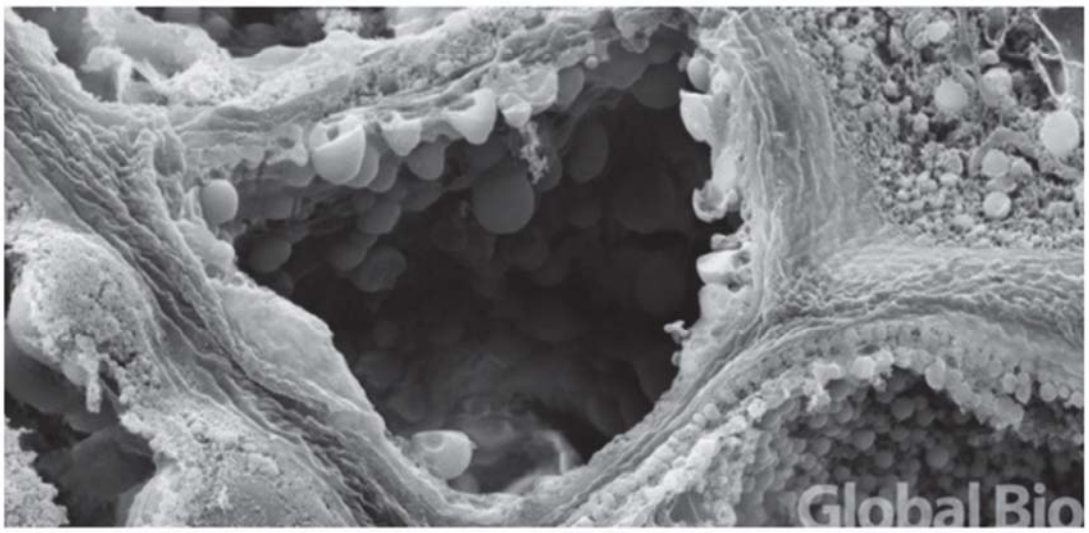


不同培養基之ESC 幹細胞能力差異

YH Huang, et al., 2009 FASEB J
YH Huang, et al., 2014 Mol Human Reprod
Kuo et al., 2018 Stem Cell Reports

《Nature》研究人員當心！癌細胞株可能與您想的不同

2018-08-13
作者: 環球生技月刊

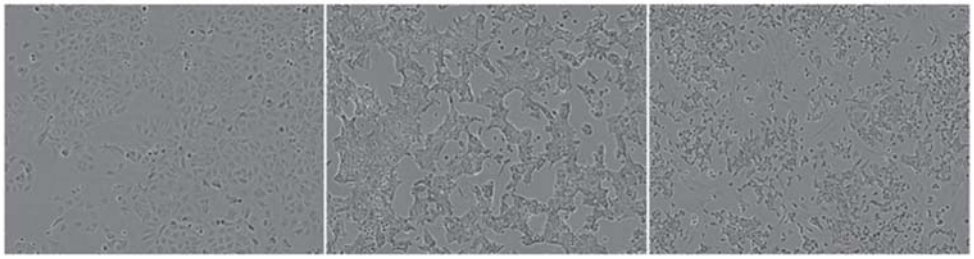


《Nature》研究人員當心！癌細胞株可能與您想的不同(圖/環球生技月刊)

不同實驗室所養的癌細胞之細胞型態與基因背景都不相同

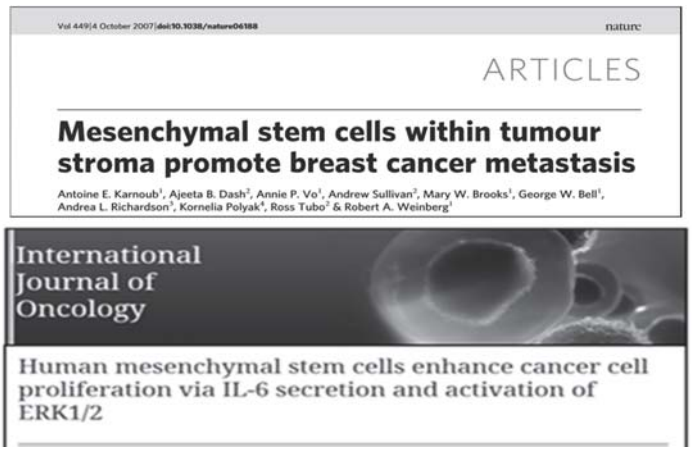
研究團隊用2種廣泛使用的細胞株進行研究：27種雌激素受體陽性乳腺癌細胞MCF-7與23種肺炎細胞株A549，分別以全基因定序(whole-genome DNA sequencing)檢測450個在癌症細胞中常突變的基因，還做了大量的單細胞RNA序列(single-cell RNA-sequencing)，每種不同的細胞株代表該品系經過不同種類的實驗室操作，不同培養時間長短以及不同的原始來源。

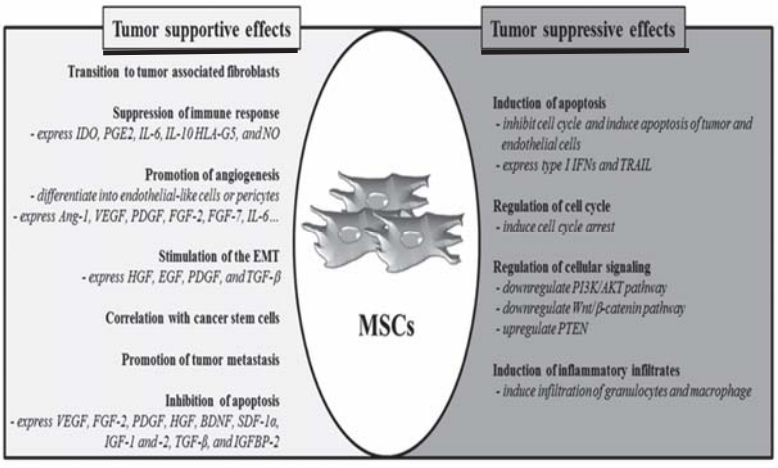
結果顯示了不同細胞株間具有高度的基因組差異，由單一點突變到大規模的基因結構改變(例如：整個染色體臂的丟失)，甚至基因表現的改變，均指向癌細胞株既不穩定且一致性也不高，這些基因改變甚至影響細胞株的成長速率、細胞大小、形狀以及其他性狀。



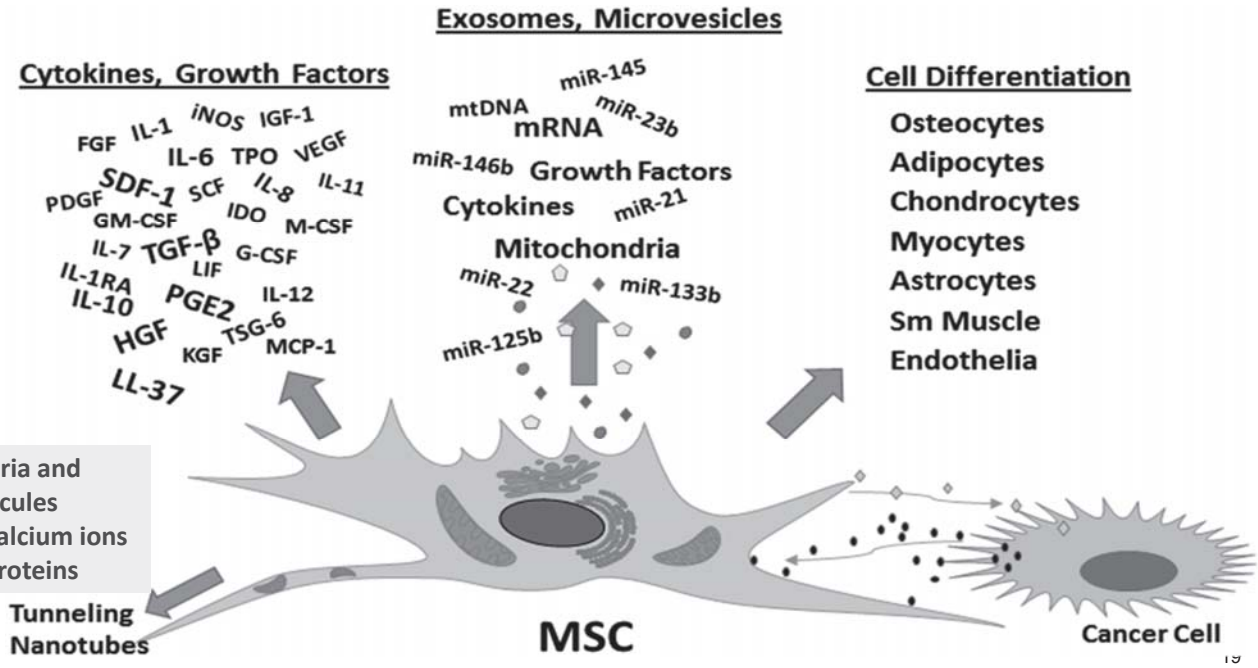
同為MCF7細胞株 卻具有不同細胞型態(圖片來源：《Nature》)

MSC Therapy Risk
間質幹細胞促進腫瘤生長之臨床治療風險





間質(幹)細胞 (MSC) 與周圍細胞之交互作用



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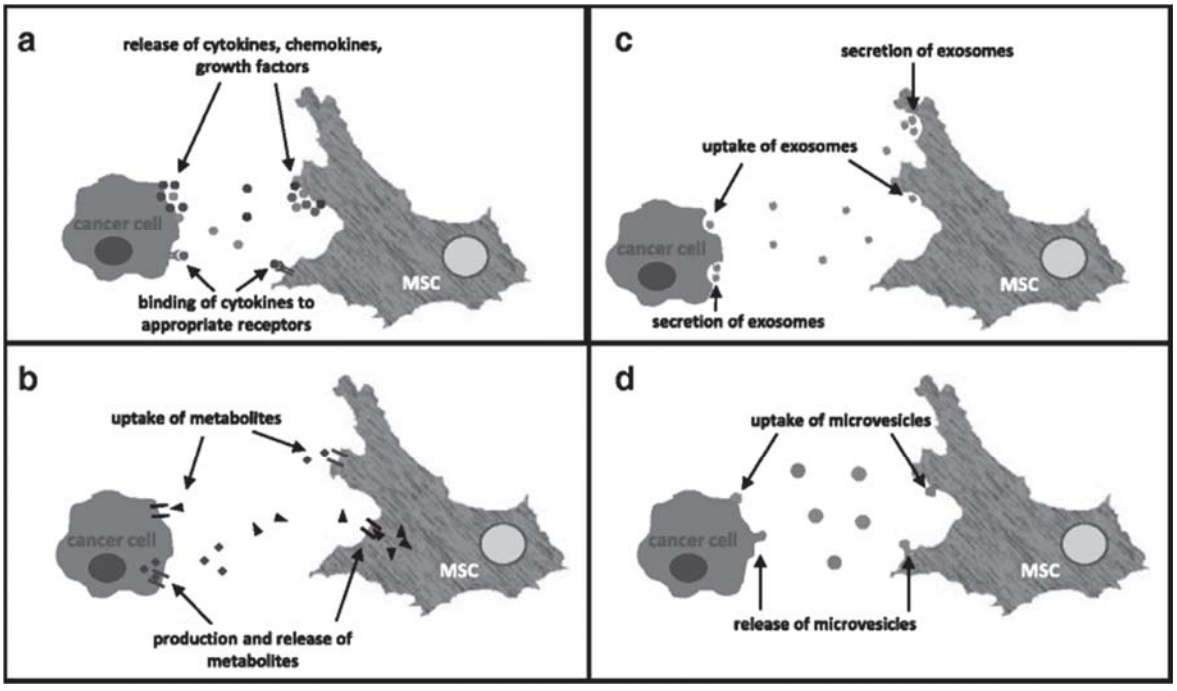
間質幹細胞 (MSC) 促進腫瘤生長方式

Interaction of MSC with tumor cells

Catharina Melzer, Yuanyuan Yang and Ralf Hass
Cell Communication and Signaling 2016 14:20
https://doi.org/10.1186/s12964-016-0143-0 | © The Author(s). 2016
Received: 28 July 2016 | Accepted: 2 September 2016 | Published: 8 September 2016



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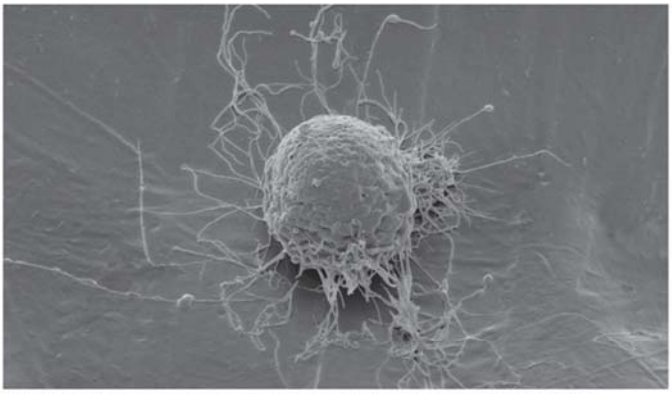


Scanning electron micrograph of what is called a human mesenchymal stem cell, which some say can develop into bone, cartilage or fat cells.

Clear up this stem-cell mess

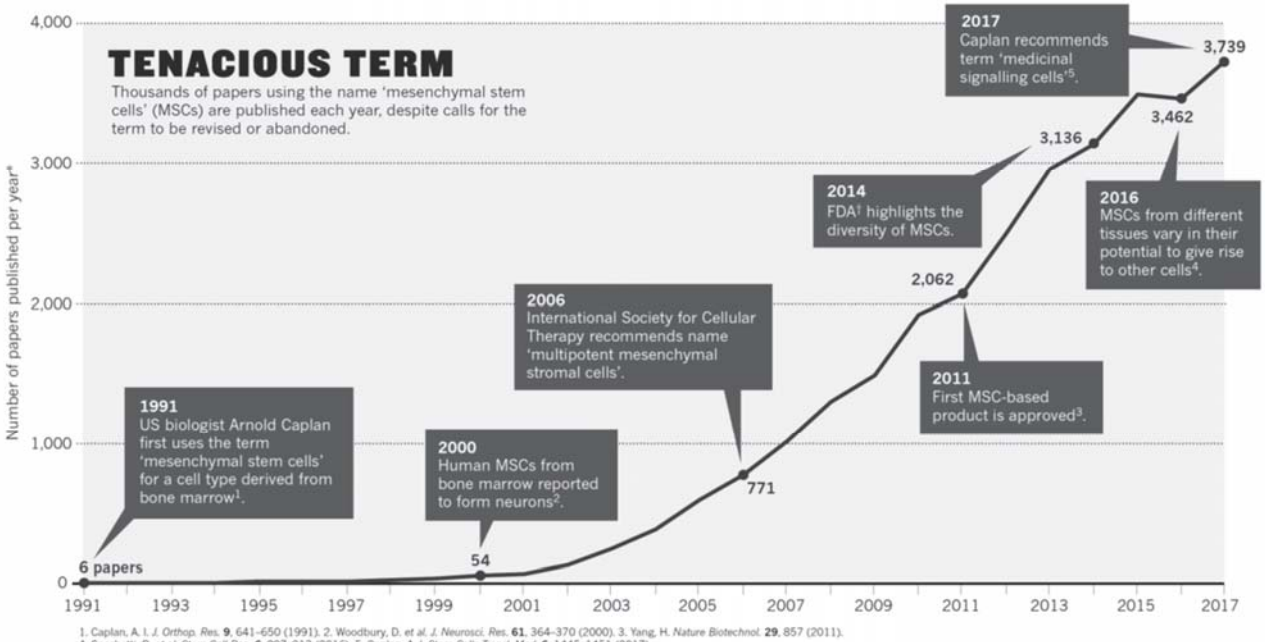
Confusion about mesenchymal stem cells is making it easier for people to sell unproven treatments, warn **Douglas Sipp**, **Pamela G. Robey** and **Leigh Turner**.

Various populations of cells in the adult human body have been the subject of controversy since the early 2000s. Contradictory findings about these haphazardly termed 'mesenchymal stem cells', including their origins, developmental potential, biological functions and possible therapeutic uses, have prompted biologists, clinicians and scientific societies to recommend that the term be revised or abandoned. Last year, Several studies indicate that the variety of cells currently dropped into the MSC bucket will turn out to be various tissue-specific cell types, including stem cells[2].

Yet the name persists despite the evidence pointing to this, and almost two decades after questions about the validity of MSCs were first raised. A literature search indicates that, over the past 5 years, more than 3,000 research articles referring to MSCs have been published every year (see 'Tenacious have helped MSCs to acquire a near-magical, all-things-to-all-people quality in the media and in the public mind[3] — hype that has been easy to exploit. MSCs have become the go-to cell type for many unproven stem-cell interventions. The confusion must be cleared up.

What is needed is a coordinated global effort to improve understanding of the biology of the cells currently termed MSCs, and a commitment from researchers, jour-

21



1. Caplan, A. I. *J. Orthop. Res.* **9**, 641–650 (1991). 2. Woodbury, D. *et al. J. Neurosci. Res.* **61**, 364–370 (2000). 3. Yang, H. *Nature Biotechnol.* **29**, 857 (2011).
4. Sacchetti, B. *et al. Stem Cell Rep.* **6**, 897–913 (2016). 5. Caplan, A. I. *Stem Cells Transl. Med.* **6**, 1445–1451 (2017).
*From PubMed search for "mesenchymal stem cells". †US Food and Drug Administration.

22

DOUBTFUL DRUGS

Clinical trials with MSCs fail to deliver

A move towards translational studies requires a robust understanding of the actual biological properties of the cell types currently called mesenchymal stem cells (MSCs).

So far, both the results and the quality of MSC-based clinical trials have been underwhelming. Take a 2014 meta-analysis of 49 trials using 'bone-marrow stem cells' (in many cases, 'bone-marrow MSCs') to treat cardiovascular disease, for instance. According to that analysis, the studies that scored better in terms of rigour were more likely to report less efficacy for MSC treatments than were those judged to be less rigorous[11].

Clinical studies using MSCs (or any stem cells) must adhere to the same standards of research design and oversight that apply to any responsible clinical trial before the cells are administered to human participants. D.S., P.G.R. & L.T.

Douglas Sipp *is a researcher at RIKEN and project professor at Keio University School of Medicine and Global Research Institute, Tokyo, Japan.* **Pamela G. Robey** *is a senior investigator at the National Institute of Dental and Craniofacial Research, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA.* **Leigh Turner** *is associate professor at the Centre for Bioethics, University of Minnesota, Minneapolis, USA.*
e-mail: sipp@cdb.riken.jp

1. Caplan, A. I. *Stem Cells Transl. Med.* **6**, 1445–1451 (2017).
2. Sacchetti, B. *et al. Stem Cell Rep.* **6**, 897–913 (2016).
3. Caulfield, T., Sipp, D., Murry, C. E., Daley, G. Q. & Kimmelman, J. *Science* **352**, 776–777 (2016).
4. Caplan, A. I. *J. Orthop. Res.* **9**, 641–650 (1991).
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6. Dominici, M. *et al. Cytotherapy* **8**, 315–317 (2006).
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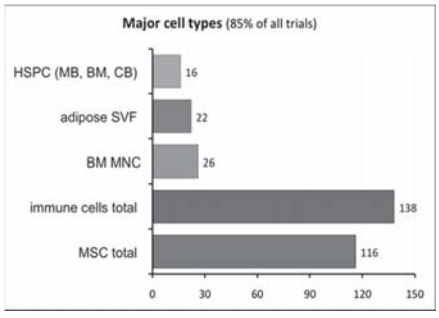
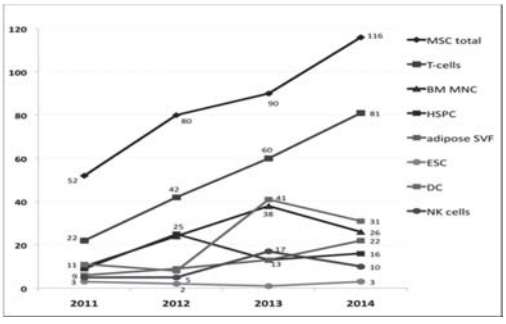
L.T. declares competing non-financial interests; see go.nature.com/2pjhdai for details.

Immune Cell Cancer Therapy



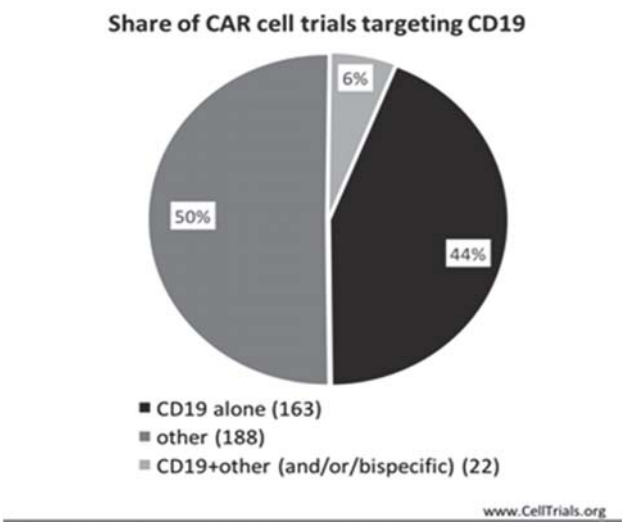


CAR-T

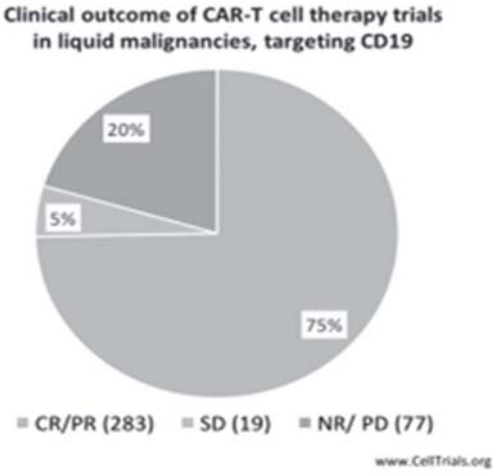
EMBO reports (2007) 8, 1024-1030

CART Clinical Trials on CD19 are of Efficacy

50% of all registered CAR cell trials are targeting CD19

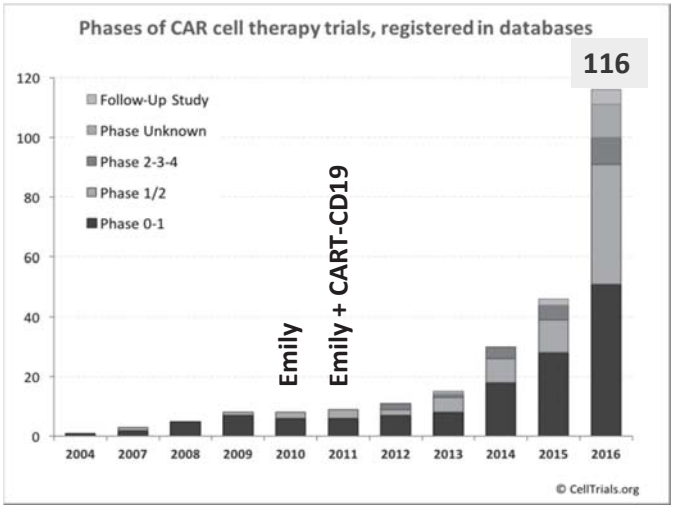


80% of all registered CD19 CAR cell trials are CR/PR or SD

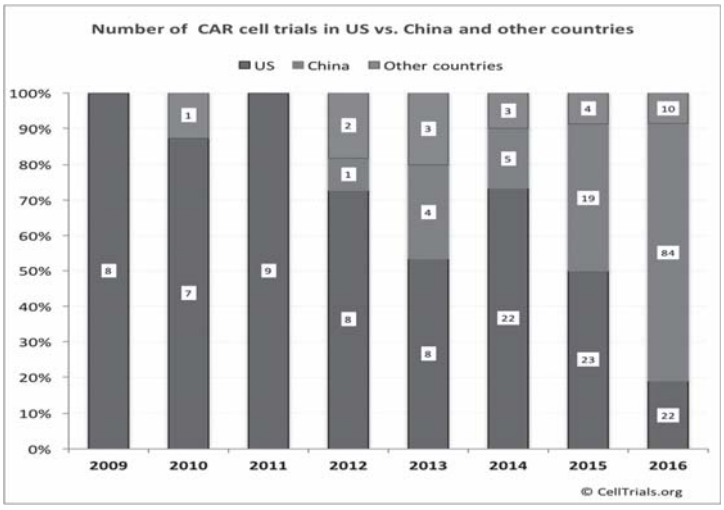


Total number of CD19 publications 25, total number of evaluable patients: 379 (as of Sep 1, 2017).

Immune Cellular Therapy CT Worldwide (Till 2016)



Phases of CAR cell therapy trials registered worldwide Bersenev, Alexey **(2017)**



1. Total number of CAR cell therapy trials in China until **2016 was 113 (China).**
2. **38 academic institutions and hospitals** were identified as sponsors of CAR cell therapy trials **in China**.

CART Clinical Risk

USA Juno Therapeutics Terminated CART Clinical Trails in 2016 Dec

December, 2016


FORTUNE

Juno Therapeutics' Shares Sink After 2 More Deaths in Leukemia Drug Trial

by Reuters

The total number of deaths is now five.
2016年已有五位死亡案例
Juno Therapeutics said two more patients had died after suffering brain swelling during a trial of its experimental genetically engineered leukemia drug, bringing the total up to five.

FDA Approves First Gene Therapy For Leukemia (August 30, 2017)
Kymriah, CART Therapy (CTL019, $475,000 per treatment)

Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice

AUG 30, 2017

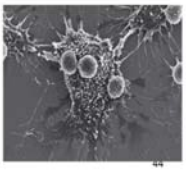

Kymriah™ Product Shot

FDA Approves 2nd Gene Therapy For DLBCL

Kite Pharma **Kite Pharma (October 18, 2017), Kymriah (May 3, 2018)**

美東時間18日，美國食品藥物管理局(FDA)宣佈，Kite Pharma旗下CAR-T療法 Yescarta (axicabtagene ciloleucel) 獲准上市，用於治療罹患特定類型的瀰漫性大型B細胞淋巴瘤(DLBCL)成人患者。這些患者至少曾接受兩次其他治療，但病程未出現緩解，或是產生復發。

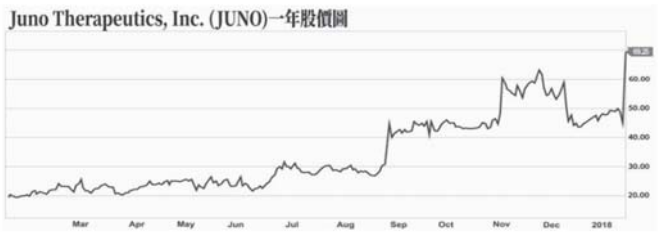
這是美國FDA第一次針對特定非何杰金氏淋巴瘤的CAR-T療法，也是全球第二款獲准上市的CAR-T療法。



CART Clinical Risk

USA Juno Therapeutics Terminated CART Clinical Trails in 2016 Dec

Jan 22nd, 2018



Juno Therapeutics, Inc stock price is quickly going up in 2017!!

May 6, 2018

Celgene

Mar 6, 2018

Celgene buy Juno for $9 billion USD.

Celgene Completes Acquisition of Juno Therapeutics, Inc., Advancing Global Leadership in Cellular Immunotherapy

Advances Strategy to Become a Leader in Global Cellular Immunotherapy

Immediately Adds Late-Stage Therapy JCAR017, an Expected Growth Driver From 2020 and Beyond with Potential Global Peak Sales of Approximately $3B

Kymriah和 Yescarta CAR-T療法同時獲歐洲市場許可

August 28, 2018

NOVARTIS

Our Company | Our Focus | Our Science | Join Us

Novartis receives European Commission approval of its CAR-T cell therapy, Kymriah® (tisagenlecleucel)

Aug 27, 2018

- *The EC approval is based on the first global CAR-T registration trials, which included patients from eight European countries and demonstrated durable responses and a consistent safety profile in r/r pediatric B-cell ALL and r/r DLBCL*
- *Novartis is the only company with an approved CAR-T cell therapy for pediatric r/r B-cell ALL and the first to receive approval in two distinct indications, both in the EU and the US*

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Keyword

Search

Yescarta® (Axicabtagene Ciloleucel) Receives European Marketing Authorization for the Treatment of Relapsed or Refractory DLBCL and PMBCL, After Two or More Lines of Systemic Therapy

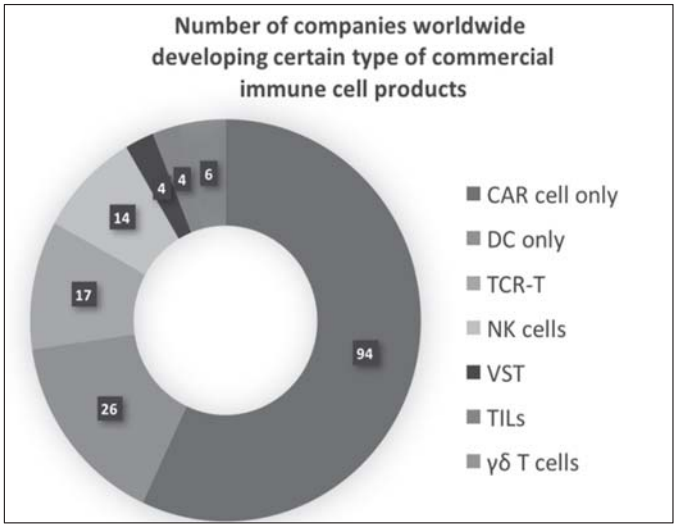
PDF Download

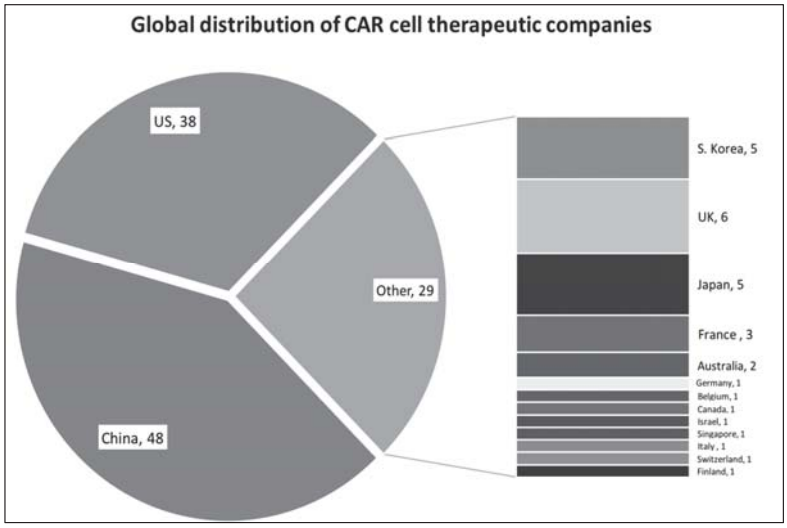
– New Option for Adult Patients in Europe as Axicabtagene Ciloleucel Becomes the First CAR T to Receive European Approval for Two Types of Aggressive Non-Hodgkin Lymphoma –

SANTA MONICA, Calif.--(BUSINESS WIRE)--Aug. 27, 2018-- Kite, a Gilead Company (Nasdaq: GILD), today announced that the European Commission (EC) has granted Marketing Authorization for Yescarta® (axicabtagene ciloleucel) as a treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. The Marketing Authorization approves axicabtagene ciloleucel for use in the 28 countries of the European Union, Norway, Iceland and Liechtenstein.

This press release features multimedia. View the full release here:

Global CART Cell Therapeutic Company (Till 2018)



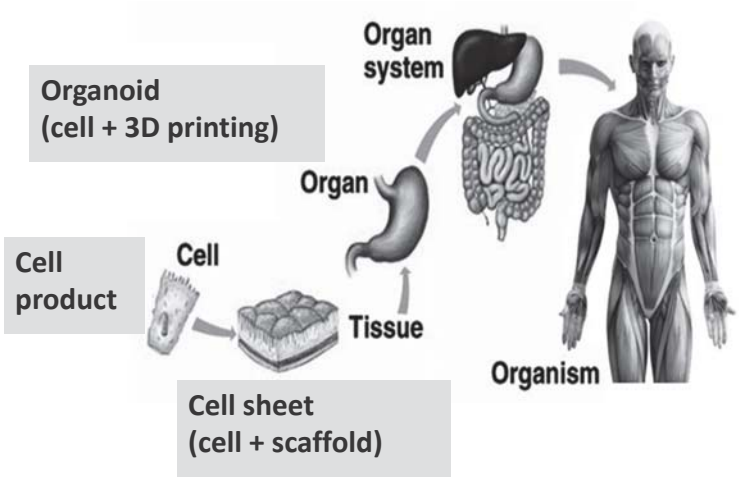


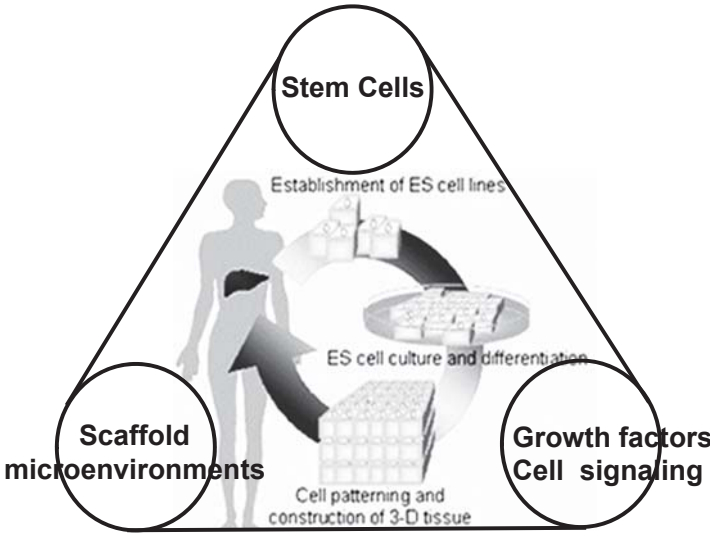
1. A total number of companies in the dataset is **215**.
2. There are **68** companies (**1/3 of all immunocellular companies worldwide**) only in China.

未來中國很可能在細胞免疫療法領域取得世界領導地位. No CART company in Taiwan (2018)

A BERSENEV **FEBRUARY 2, 2018/115 Companies**

Cell Therapy and Regeneration Medicine





Stem Cell-based Tissue Engineering

First human transplantation of a bioengineered airway tissue

Paolo Macchiarini, MD, PhD,[a,b] Thorsten Walles, MD,[a,b] Christian Biancosino,[b] and Heike Mertsching, PhD,[b]
Hannover, Germany

638 The Journal of Thoracic and Cardiovascular Surgery • October 2004

The story of Claudia Castillo

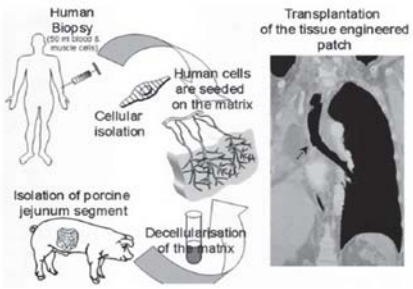
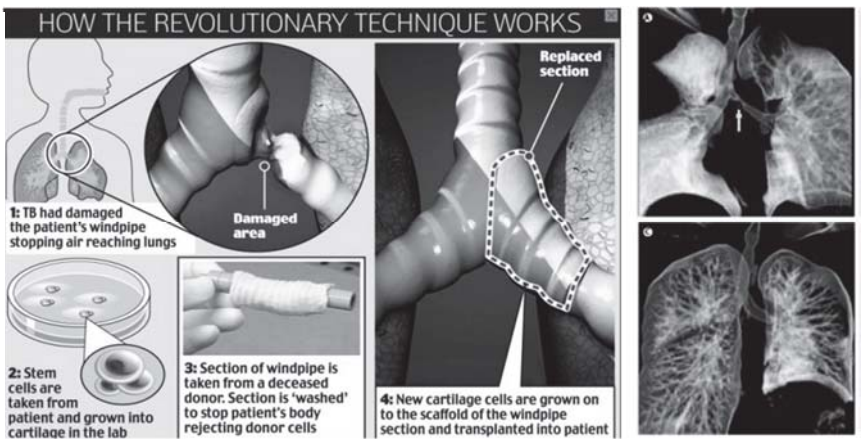


Figure 1. Process of engineering the bioartificial patch. Muscle cells and fibroblasts are isolated from a biopsy specimen obtained from the patient. These cells are seeded on a biologic matrix representing a collagen network generated from a decellularized porcine jejunal segment. During the incubation period, the cells start to remodel the xenogenic matrix and replace it with autologous connective tissue. Within 4 weeks, this autologous bioartificial implant can be clinically used. The computed tomographic scan of the chest 6 weeks after graft implantation shows the site *(arrow)* where the tissue-engineered patch was transplanted. The right pleural cavity is completely filled with the transposed omentum major and right subscapular muscle.



Paolo Macchiarini., et al.
Clinical transplantation of a tissue-engineered airway. *Lancet*, 2008

2014

The first tissue-engineered airway transplantation: 5-year follow-up results

Alessandro Gonfiotti, Massimo O Jaus, Daniel Barale, Silvia Baiguera, Giovanni Rombolà, Philipp Jungebluth, Paolo Macchiarini

- 2008: Implanted World's First Donor Trachea
- Recipient: Claudio Castillo
- Survived Procedure — Now Has Normal Respiratory Function

Lancet 2014; 383: 238–44
Published Online October 23, 2013

Summary

Background In 2008, the first transplantation of a tissue-engineered trachea in a human being was done to replace an end-staged left main bronchus with malacia in a 30-year-old woman. We report 5 year follow-up results.

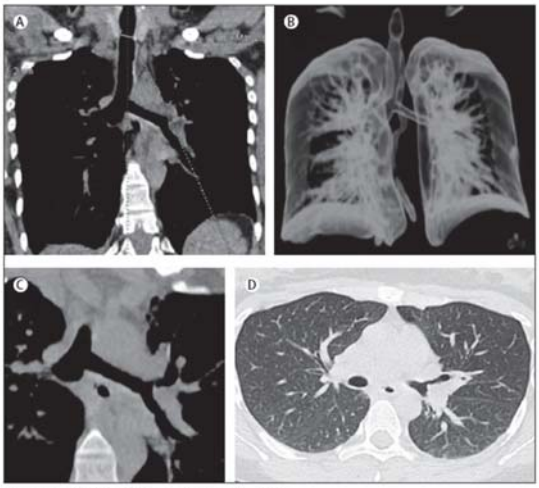


Figure 2: **Imaging findings at 5 years after transplantation**
Multidetector CT scan (March, 2013) showing the entire graft with a normal proximal anastomosis; (A) coronal view, (B) 3D reconstruction. Multidetector CT scan (March, 2013) showing a normal distal anastomosis (C) with a normal inflated lung (D).

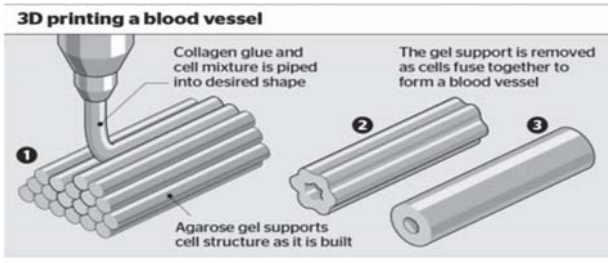
Artificial trachea researcher responds to misconduct report
June 26,,2015

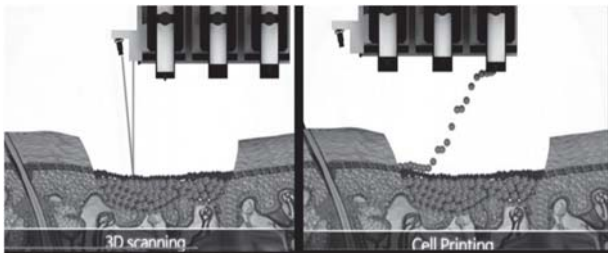
Regenerative Medicine Researcher Cleared of Scientific Misconduct Charges
Aug. 28, 2015

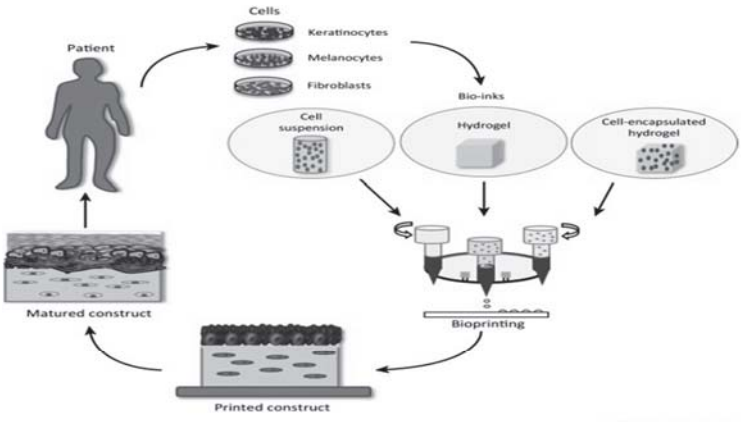
Macchiarini P (2011). "Bioartificial tracheobronchial transplantation. Interview with Paolo Macchiarini". *REGENERATIVE MEDICINE* **6** (6 Supplement): 14–15.

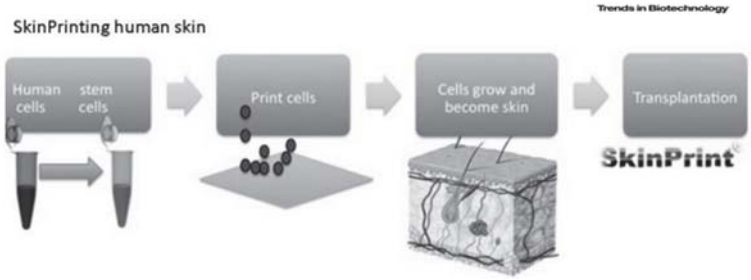
2016

3D Bioprinting and Regeneration Medicine



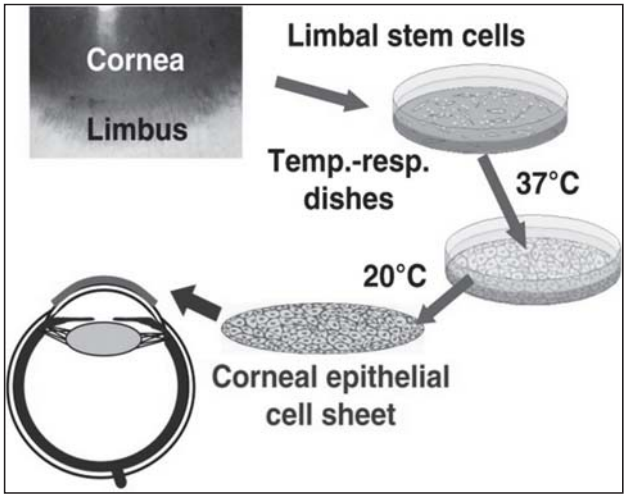


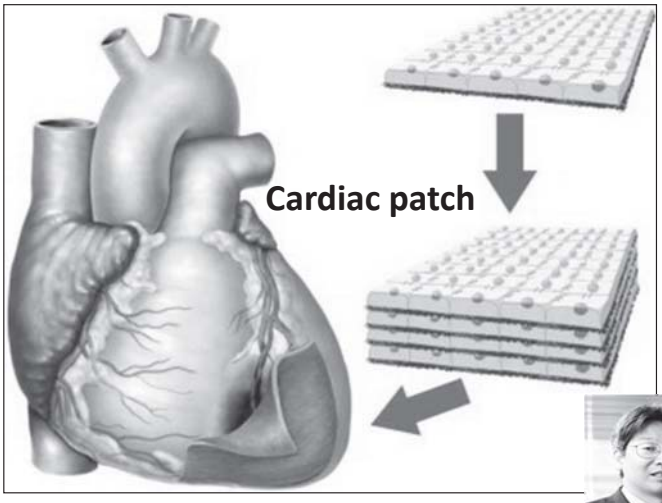




Cell Sheet and Regeneration Medicine
細胞層片與再生醫學

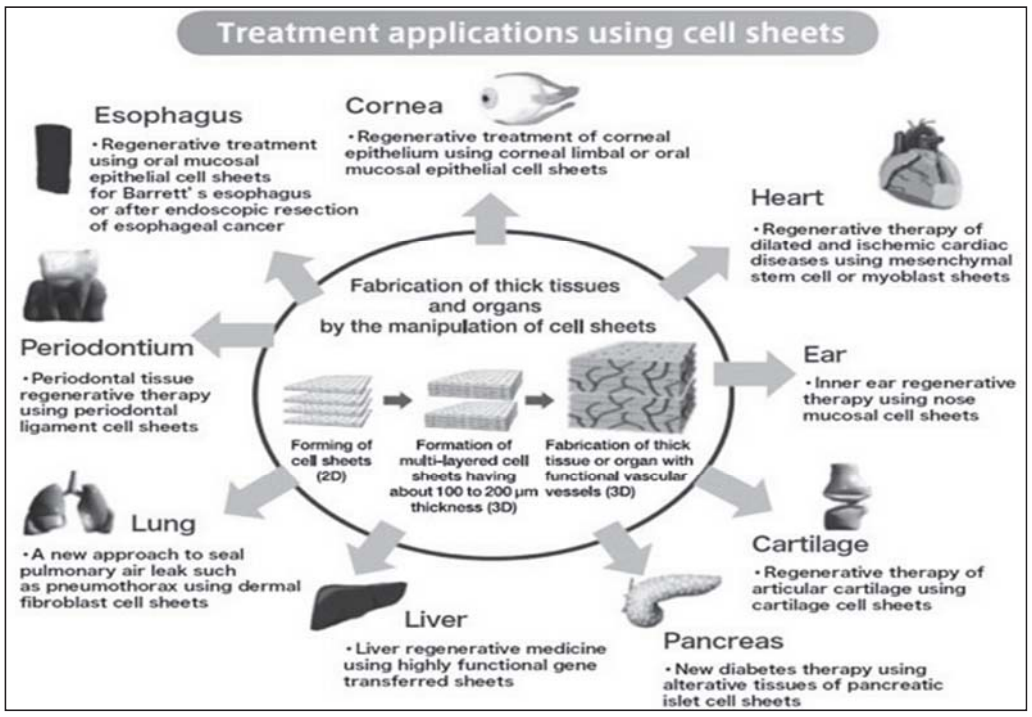
Prof. Teruo OKANO 岡野光夫教授　**Prof. Tatsuya SHIMIZU清水達也教授**



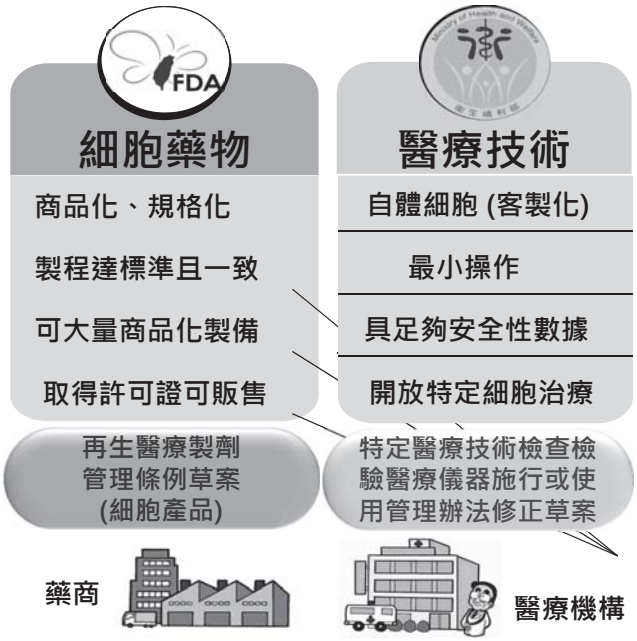


東京女子醫科大學先端生命醫科學研究所

細胞層片與再生醫學



2018 台灣細胞治療與再生醫學法規大躍進
細胞藥物產品 vs. 醫療技術
完善分工



細胞治療特管辦法20180906 施行

附表三

項目名稱	適應症
一、自體 CD34+ selection 周邊血幹細胞移植	一、血液惡性腫瘤（hematological malignancies）： （一）白血病（不包括慢性骨髓白血病之慢性期）。 （二）淋巴瘤。 （三）多發性骨髓瘤。 二、慢性缺血性腦中風。 三、嚴重下肢缺血症。
二、自體免疫細胞治療（包括 CIK、NK、DC、DC-CIK、TIL、gamma-delta T 之 adoptive T 細胞輸入療法）	一、血液惡性腫瘤（hematological malignancies）經標準治療無效。 二、第一至第三期實體癌（solid tumor），經標準治療無效。 三、實體癌第四期。
三、自體脂肪幹細胞移植 ★	一、慢性或滿六週未癒合之困難傷口。 二、占總體表面積百分之二十（含）以上之大面積燒傷或皮膚創傷受損。 三、皮下及軟組織缺損。 四、退化性關節炎及膝關節軟骨缺損。 五、其他表面性微創技術之合併或輔助療法。
四、自體纖維母細胞移植 ★	一、皮膚缺陷：皺紋、凹洞及疤痕之填補及修復。 二、皮下及軟組織缺損。 三、其他表面性微創技術之合併或輔助療法。
五、自體骨髓間質幹細胞（bone marrow mesenchymal stem cell）移植 ★	一、退化性關節炎及膝關節軟骨缺損。 二、慢性缺血性腦中風。 三、骨髓損傷。
六、自體軟骨細胞移植	膝關節軟骨缺損。

2018 MOHW
細胞治療特管辦法
(第十二條)

Special Management Regulation Amendment

第二章　特定醫療技術		章名新增。
第一節　細胞治療技術		節名新增。
第十二條　醫院或具特殊專長經中央主管機關同意之醫療機構（以下併稱特定機構），始得施行細胞治療技術。	規範醫療機構與施行醫師	一、本條新增。 二、明定可施行細胞治療技術之醫療機構。
第十三條　特定機構施行附表一所列細胞治療技術，應擬訂計畫，向中央主管機關申請核准後，始得為之。 前項計畫，應載明下列事項： 一、施行機構。 二、項目。 三、適應症。 四、施行醫師。 五、實施方式。 六、治療效果之評估及追蹤方式。 七、費用及其收取方式。 八、同意書範本。 九、細胞操作之儀器及實驗室。 十、細胞製造管制資料之方式。 十一、發生不良反應之救濟措施。	無規範廠商條例	一、本條新增。 二、醫療機構可施行之細胞治療技術及其適應症，明定於附表一。 三、醫療機構申請施行細胞治療技術應擬訂計畫，計畫書並應載明相關事項，向中央主管機關申請核准。

細胞治療產品--非最小操作 (細胞培養)
人類細胞治療產品臨床試驗及查驗登記審查基準

1. 細胞培養 (細胞與幹細胞)– 細胞培養液、添加生長因子
2. 血清(影響細胞效價與病毒汙染)
3. 細胞培養環境 (氧氣、溫度)
4. 細胞細代數
5. 細胞冷凍儲存抗凍劑殘留量
6. 細菌汙染
7. 黴漿菌汙染
8. 病毒汙染
9. 內毒素
10. 抑菌性與抑黴菌性
11. 細胞存活率與特性之穩定度
12. 細胞功能效價

自體細胞
最小操作
具足夠安全性臨床數據

2018 MOHW
細胞治療特管辦法
(第十三條)

Special Management Regulation Amendment

第十四條　特定機構擬施行附表一以外之細胞治療技術，應依醫療法規定申請施行人體試驗，或擬訂計畫，向中央主管機關申請核准後，始得為之。 前項計畫，應載明下列事項： 一、施行機構。 二、項目。 三、適應症。 四、施行醫師。 五、實施方式。 六、治療效果之評估及追蹤方式。 七、費用及其收取方式。 八、已發表之國內、外相關文獻報告。 九、同意書範本。 十、細胞操作之儀器及實驗室。 十一、細胞製造管制資料之方式。 十二、發生不良反應之救濟措施。	**專案審查** **專屬特定機構執行**	一、本條新增。 二、因應新細胞治療技術發展，國外已施行、風險性低，或是經人體試驗確定安全性，成效可預期，未列於附表一之細胞治療技術，可由醫療機構提出申請，新增附表一之細胞治療項目及適應症，並同時核准該醫療機構之施行計畫，以簡化行政程序，加速新細胞治療技術之臨床應用。 三、本條所定計畫應載明事項，應包含國內、外相關文獻報告。

自體細胞
最小操作
具足夠安全性臨床數據

SPECIAL REPORT

Balancing Safety and Innovation for Cell-Based Regenerative Medicine

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