核准之再生製劑介紹

財團法人醫藥品查驗中心
Center for Drug Evaluation,Taiwan

醫藥品查驗中心
諮詢輔導組
王亞蕾 醫師

2024/07/14

大綱

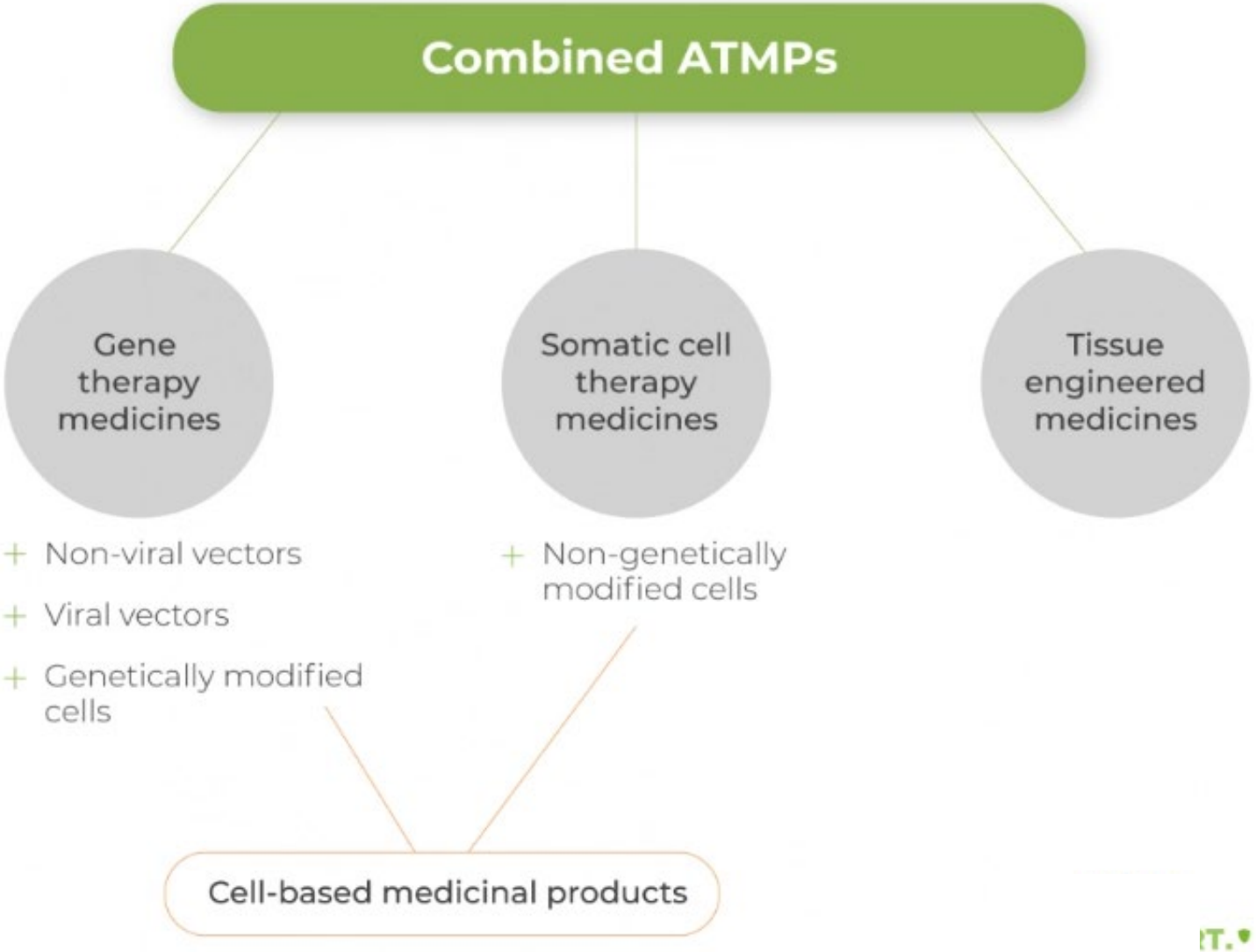
- 再生醫療製劑範疇
- 國內外已核准再生醫療製劑
- 基因治療以及CAR-T
- 細胞治療

再生醫療製劑範疇

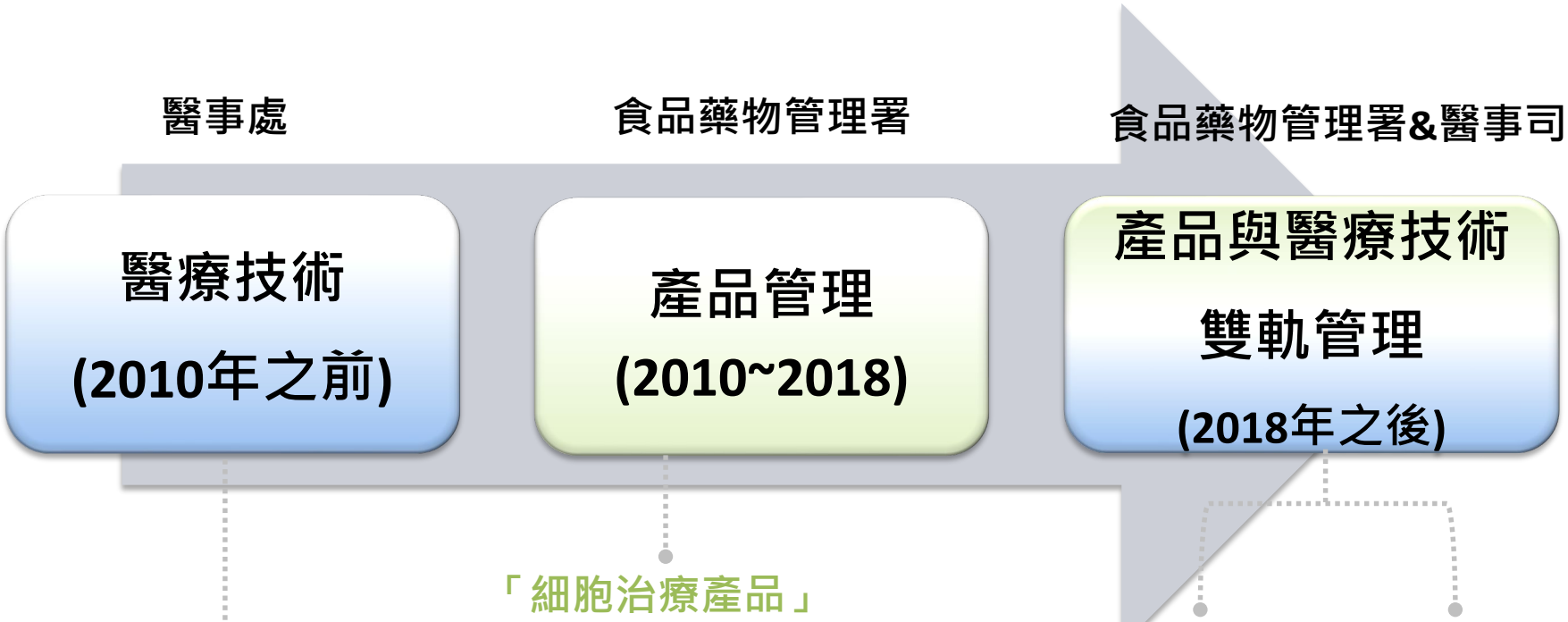
財團法人醫藥品查驗中心
Center for Drug Evaluation,Taiwan

再生醫療製劑

- 結合分子遺傳學、基因工程、細胞療法、生醫材料及組織工程的新興跨學科領域
- 目的：修復或替代因年齡、疾病、先天缺陷或後天損傷而導致受損的組織或器官
- 特色：regeneration
- 主要類別為細胞治療以及基因治療、組織工程產品


Combined ATMPs
Gene therapy medicines
Somatic cell therapy medicines
Tissue engineered medicines
+ Non-viral vectors
+ Viral vectors
+ Genetically modified cells
+ Non-genetically modified cells
Cell-based medicinal products

再生醫療管理沿革



財團法人醫藥品查驗中心
Center for Drug Evaluation,Taiwan

細胞治療法規管理沿革

本院新聞

確保再生醫療品質及維護病人權益 政院通過「再生醫療法」及「再生醫療製劑條例」草案

日期：112-02-16　　資料來源：新聞傳播處

為確保再生醫療的品質、安全及有效性，並維護病人權益，行政院會今（16）日通過衛生福利部擬具的「再生醫療法」及「再生醫療製劑條例」草案，將函請立法院審議。

行政院長陳建仁表示，近年來全球受疫情影響，凸顯生醫產業的重要性，也印證生技醫療在國家安全的重要戰略定位。蔡英文總統已於2020年將「臺灣精準健康產業」列為六大核心戰略產業，再生醫療即是推動的重點項目之一。

陳院長指出，新興生醫科技發展迅速，再生醫療相關領域的技術與知能已逐漸成熟，本次「再生醫療法」及「再生醫療製劑條例」立法，將有助於建構臺灣整體再生醫療生技創新及推動方針、促進再生醫療領域發展，並加速再生醫療研發成果擴大應用至臨床醫學、強化再生醫療技術與製劑之管理與銜接，對於確保再生醫療的品質、安全及有效性，以及維護病人權益，至為關鍵。本兩項草案函請立法院審議後，請衛福部與立法院朝野各黨團溝通協調，早日完成立法程序。

再生雙法架構 (2024/6/4經立法院三讀通過)

再生醫療法

規範再生醫療執行之行為

再生醫療製劑條例

製劑全生命週期管理

再生醫療法 vs 再生醫療製劑條例

	衛福部	食藥署
	再生醫療法	再生醫療製劑條例 藥事法特別法
特性	個人化	商業化
申請者	醫療機構	藥商
申請文件	申請文件及規範依據再生醫療法及其相關辦法	臨床試驗、查驗登記相關文件
規範		需符合GMP 、 GDP
核准	特定醫療機構對個體病人執行再生醫療技術	上市許可

再生醫療製劑相關演講 - 再生醫療製劑管理專區 - 藥品 - 業務專區 - 衛生福利部食品藥物管理署 (fda.gov.tw)

再生醫療製劑與技術之定義

- 「再生醫療法」：「再生醫療」指利用基因、細胞及其衍生物，用以治療、修復或替換人體細胞、組織及器官之製劑或技術。
  - 「再生醫療製劑」指含有基因、細胞及其衍生物，供人體使用之製劑。
  - 「再生醫療技術」指於人體執行再生醫療之技術。但不包括：（一）輸血（二）使用血液製劑（三）骨髓造血幹細胞移植、周邊血造血幹細胞移植（四）人工生殖(五)其他經中央主管機關公告之技術。

依風險等級劃分管理

再生醫療製劑條例立法目的及管理範疇

考量

- 鑒於再生醫療製劑成分異質性、製程特殊性及治療複雜性
- 風險管控有別於化學或生物製劑
- 兼顧國內產業發展趨勢，建構符合我國實務管理架構

立法目的

- 確保再生醫療製劑之品質、安全及有效性
- 維護病人接受治療之權益

管理範疇

- 細胞治療製劑
- 基因治療製劑
- 組織工程製劑
- 前三款與醫療器材屬性之結構材料嵌合者

規範商品化、規格化、製程加工達標準且一致化的再生醫療製劑。

再生醫療製劑相關演講 - 再生醫療製劑管理專區 - 藥品 - 業務專區 - 衛生福利部食品藥物管理署 (fda.gov.tw)

再生醫療製劑條例-管理範疇

再生醫療製劑

基因治療	• 將重組基因嵌入或輸注人體內，以治療、預防或診斷疾病之製劑
細胞治療	• 將細胞或其衍生物加工製造，以治療、預防或診斷疾病之製劑
組織工程	• 將含有經加工、改造之組織或細胞，修復、再生或替代人體組織、器官之製劑
複合製劑	• 將具有醫療器材屬性之結構材料，嵌合前三款全部或部分之製劑

Reference:再生醫療製劑條例草案

再生醫療製劑條例-管理範疇

再生醫療製劑條例立法重點

藥事法特別法

- 明定**有附款許可**，鼓勵產業發展，使民眾及早取得再生醫療新藥。
- 訂定**組織、細胞提供者合適性判定**、**知情同意**、**招募廣告**規定。
- 訂定再生醫療製劑**安全監視管理及流向管理**規定。
- 本條列未規定者，依藥事法及其他相關法律規定辦理。

有附款許可

- 診治**危及生命或嚴重失能**之疾病
- 完成**第二期臨床試驗**，並經審查風險效益，具安全性及初步療效者
- 經**再生醫療審議會之審議**
- 有效期間**不超過五年**，須**履行附款義務**
  - 期滿不得展延

再生醫療製劑相關演講 - 再生醫療製劑管理專區 - 藥品 - 業務專區 - 衛生福利部食品藥物管理署 (fda.gov.tw)

國內外已核准再生製劑產品

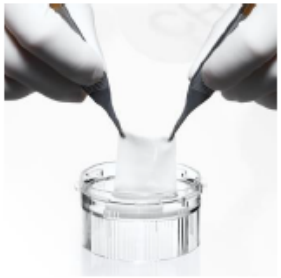
再生醫療製劑重要里程碑

基因治療蓬勃發展

1997

US FDA核准
世界第一個
細胞治療
Carticel®
自體培養軟骨細胞，
用於修復軟骨損傷。

2012



EMA核准
第一個組織工程
MACI®
(FDA2016核准)
以豬膠原蛋白膜進行
自體軟骨細胞培養，
治療成人膝關節軟骨
缺損。

2012

EMA核准
第一個基因治療
Glybera®
以AAV作為載體的脂
蛋白脂肪酶基因，治
療罕見遺傳性脂蛋白
脂酵素缺乏症。

2017

KYMRIAH® (tisagenlecleucel) Dispersion for IV infusion

YESCARTA

US FDA核准
第一個CAR-T
Kymriah®

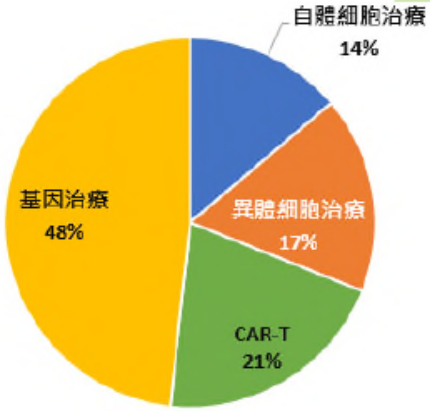
2018~

CAR-T therapy
- Tecartus
- Abecma
- Breyanzi
- Carvykti

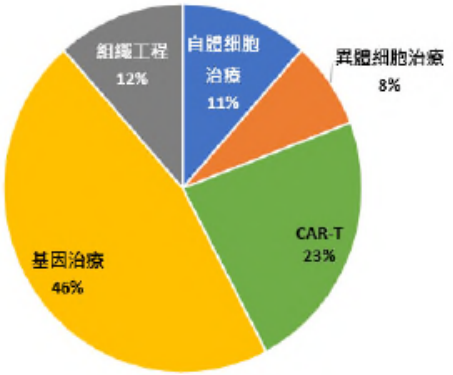
Gene therapy
- Luxturna
- Zolgensma
- Zynteglo
- Libmeldy
- Skysona
- Collategene
- Delytact

全球再生醫療核准現況

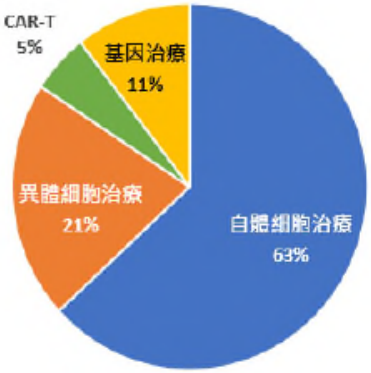
美國
自體細胞治療: 4
異體細胞治療: 5
CAR-T: 6
基因治療: 14



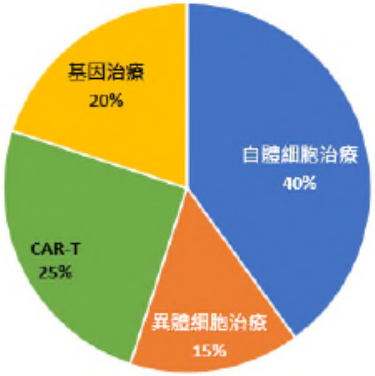
歐盟
自體細胞治療: 3
異體細胞治療: 2
CAR-T: 6
基因治療: 12
基因工程: 3



韓國
自體細胞治療: 12
異體細胞治療: 4
CAR-T: 1
基因治療: 2



日本
自體細胞治療: 8
異體細胞治療: 3
CAR-T: 5
基因治療: 4



統計至2024年4月

再生醫療製劑相關演講 - 再生醫療製劑管理專區 - 藥品 - 業務專區 - 衛生福利部食品藥物管理署 (fda.gov.tw)

US FDA (37) 再生治療核准現況(2024.06)

自體細胞治療

- Carticel (1997)
- Provenge, DC (2010)
- MACI (2016)
- AMTAGVI (2024)

異體細胞治療

- Laviv, fibrocell (2021)
- Hemacord (2011)
- Gintuit (2012)
- Ducord (2012)
- HPC, cord blood (2012)
- Allocord (2013)
- HPC, cord blood (2013)
- HPC, cord blood (2016)
- Clevecord (2016)
- Stratagraft (2021)
- Rethymic (2021)
- OMISIRGE (2023)
- LANTIDRA (2024)

基因治療

- Imlygic, T-Vec (2015)
- Kymirah (CAR-T) (2017)
- Yescarta (CAR-T) (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (CAR-T) (2020)
- Abecma (CART-T) (2021)
- Breyanzi (CAR-T) (2021)
- Carvykti (CAR-T) (2022)
- ADSTILADRIN (2022)
- HEMGENIX (2022)
- Zynteglo (2022)
- SKYSONA (2022)
- CASGEVY (2023)
- ELEVIDYS (2023)
- VYJUVEK (2023)
- ROCTAVIAN (2023)
- LYFGENIA (2023)
- BEQVEZ (2024)
- LENMELDY (2024)

我國再生醫療製劑核准現況

核准許可證

諾健生靜脈懸液注射劑 (Zolgensma)

- ✓ 基因治療製劑(109.12.22發證)
- ✓ 治療脊髓性肌肉萎縮症(SMA)

祈萊亞靜脈輸注用懸浮液 (Kymriah)

- ✓ CAR-T製劑(110.09.30發證)
- ✓ 治療急性淋巴性白血病(ALL)、瀰漫性大B細胞淋巴瘤(DLBCL)、濾泡性淋巴瘤(FL)

樂適達注射劑(Luxturna)

- ✓ 基因治療製劑(111.09.15發證)
- ✓ 治療萊伯氏先天性黑矇症 (罕病)

"諾華"樂喜達注射劑("Norvatis" Luxturna)

- ✓ 基因治療製劑(111.12.19發證)
- ✓ 治療非萊伯氏先天性黑矇症之遺傳性視網膜疾病

細胞治療 IND

103件

- Phase I: 56
- Phase I/II: 21
- Phase II: 20
- Phase III: 6

腫瘤、神經、心血管疾病為大宗

基因治療 IND

46件

- Phase I: 5
- Phase I/II: 10
- Phase II: 7
- Phase III: 17
- Phase IV: 5
- 其他: 2

罕見疾病、腫瘤為大宗

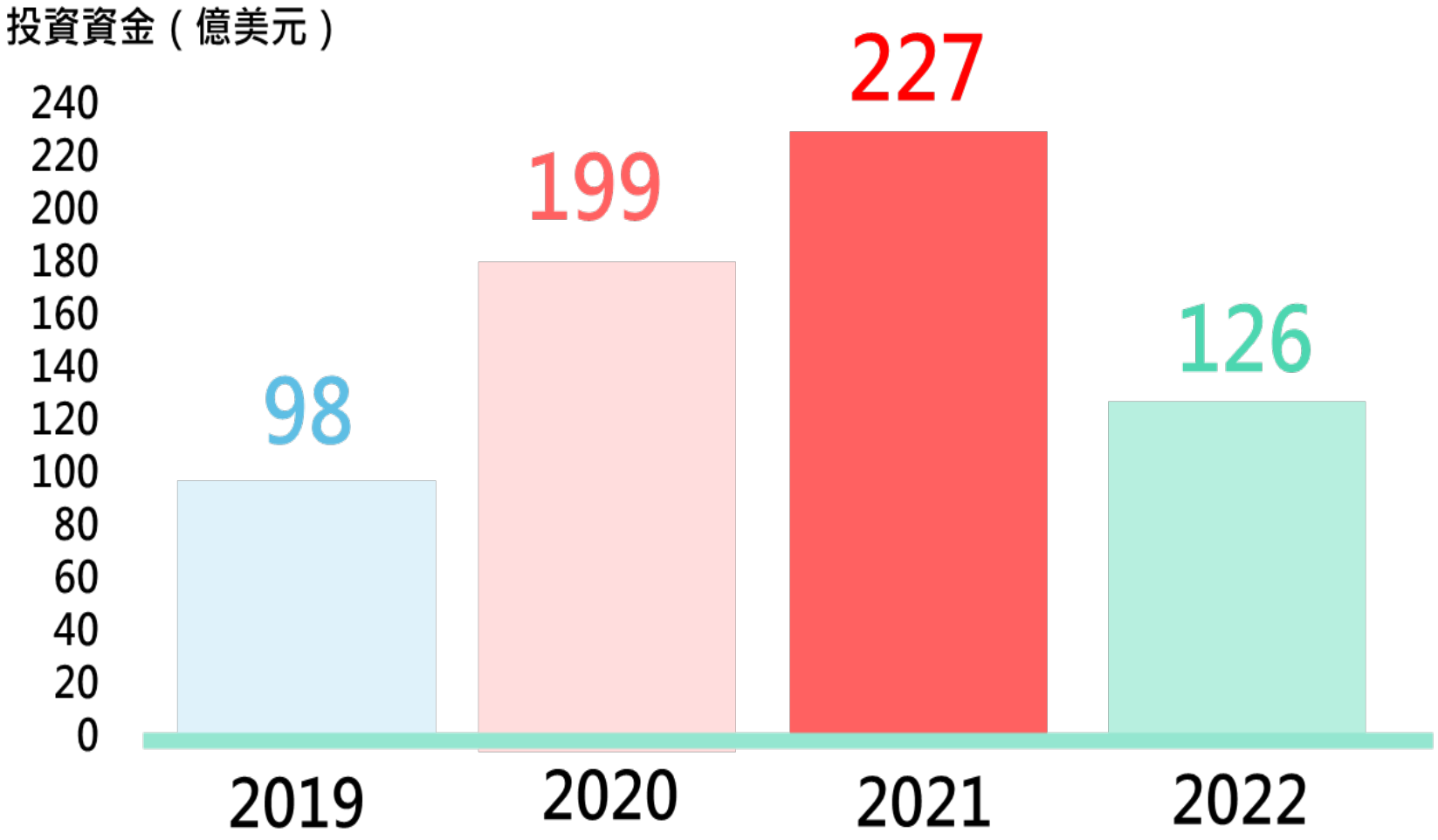
- ◆ 西藥藥品優良製造規範已增訂「附則2A:人用再生醫療製劑的製造」(111.07.27公告)
- ◆ 中華藥典第九版已收載再生醫療製劑相關通則共13項(110年出版)

統計至113年4月30日

衛生福利部 食品藥物管理署 Food and Drug Administration

再生醫療製劑相關演講 - 再生醫療製劑管理專區 - 藥品 - 業務專區 - 衛生福利部食品藥物管理署 (fda.gov.tw)

全球再生醫療投資額


投資資金（億美元）
240
220
200
180
160
140
120
100
80
60
40
20
0
98
199
227
126
2019
2020
2021
2022

全球有2093件執行中 (截至2022年第二季止)

再生醫療/先進療法之臨床試驗

776件 第一期

1117件 第二期

200件 第三期

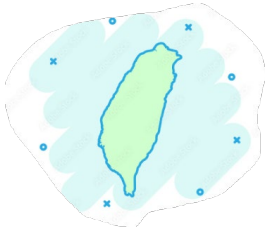
372件涉及 基因治療

721件涉及 細胞免疫腫瘤

968件涉及 細胞治療

32件涉及 組織工程

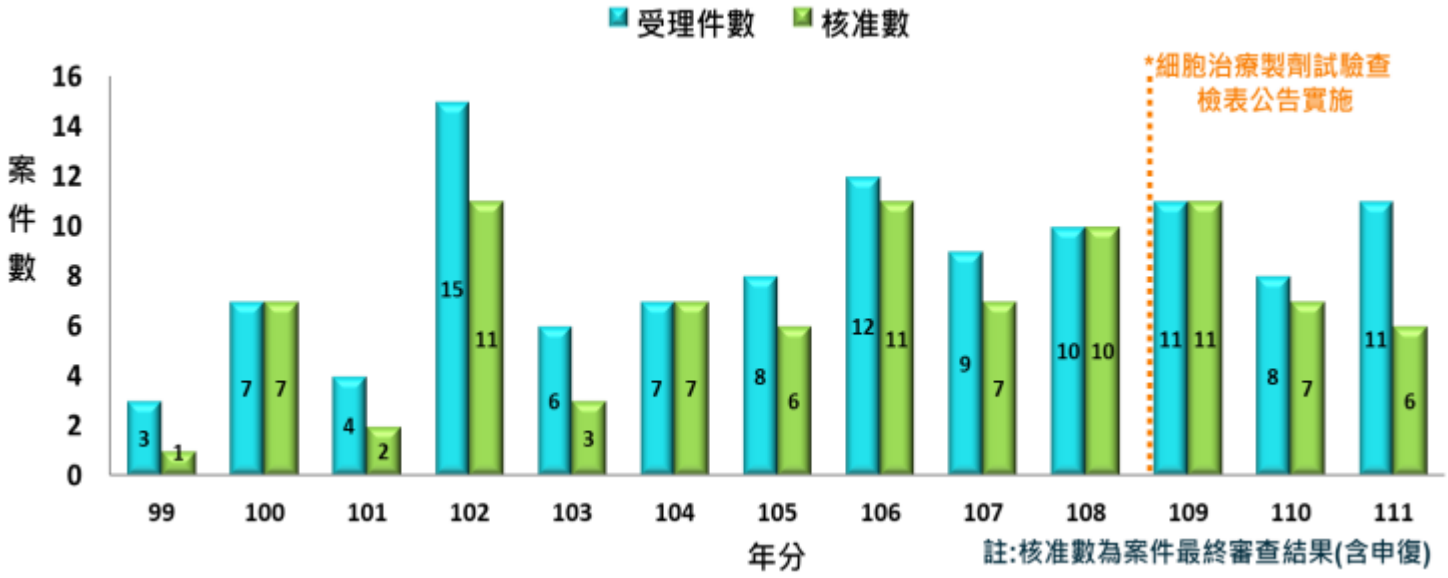
Source: Alliance for Regenerative Medicine



30件涉及基因治療

80件涉及細胞治療

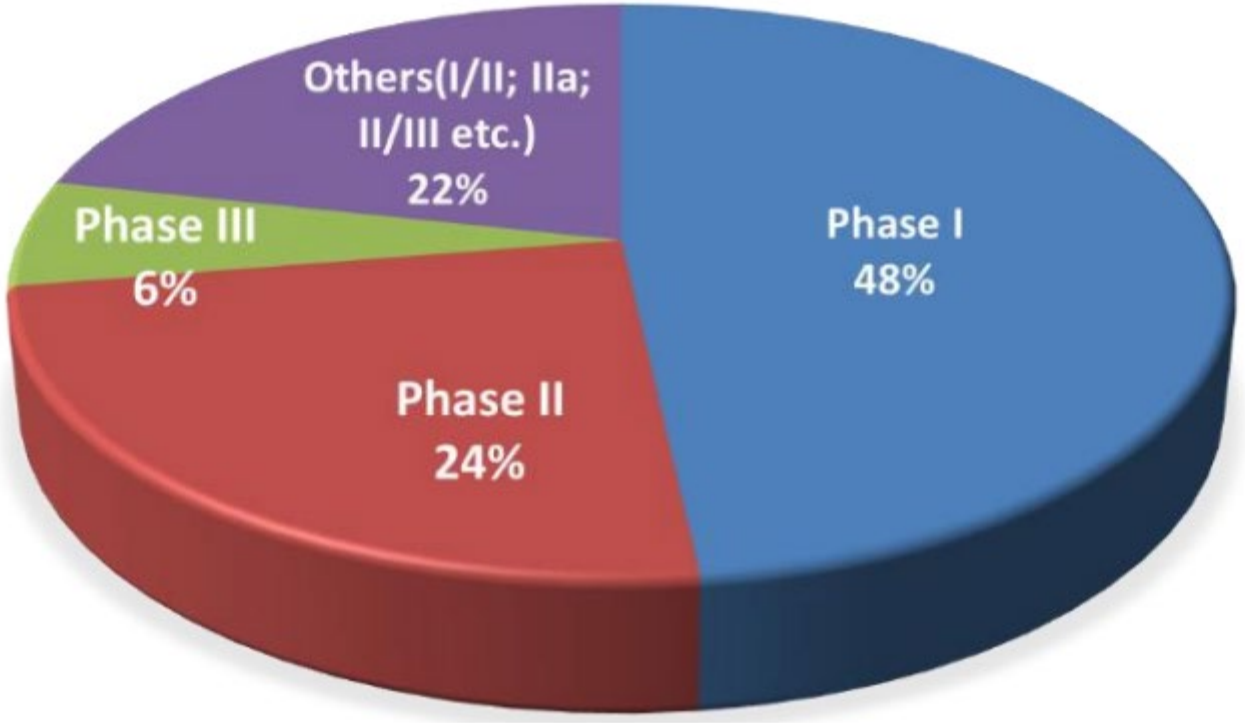
2010~2022 年細胞治療製劑臨床試驗受理及核准件數



2010~2022 年細胞治療製劑臨床試驗受理及核准件數

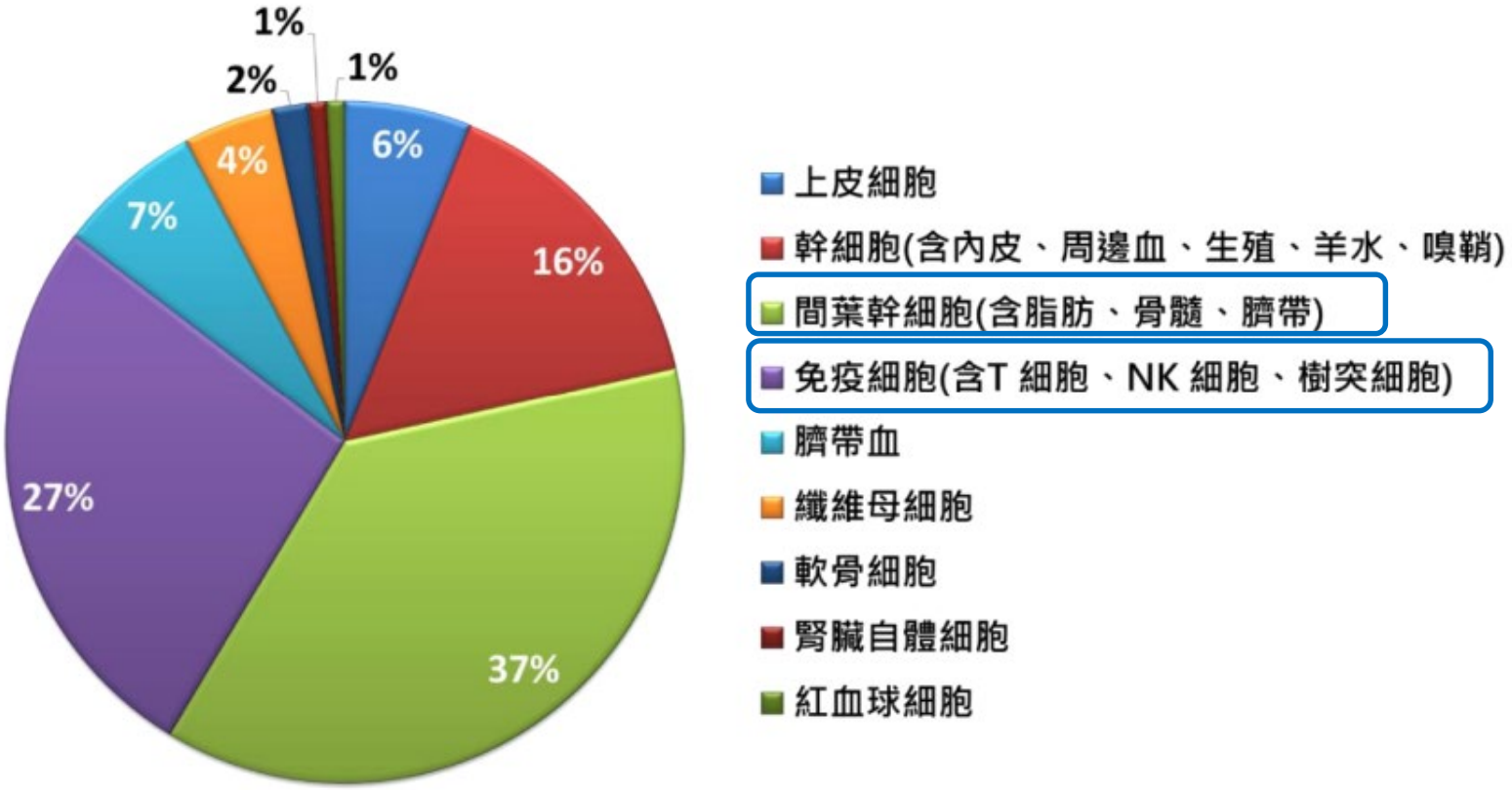
摘自當代醫藥法規月刊
RegMed 2023-07 Vol. 153

2010~2022 年細胞治療製劑臨床試驗之試驗期程



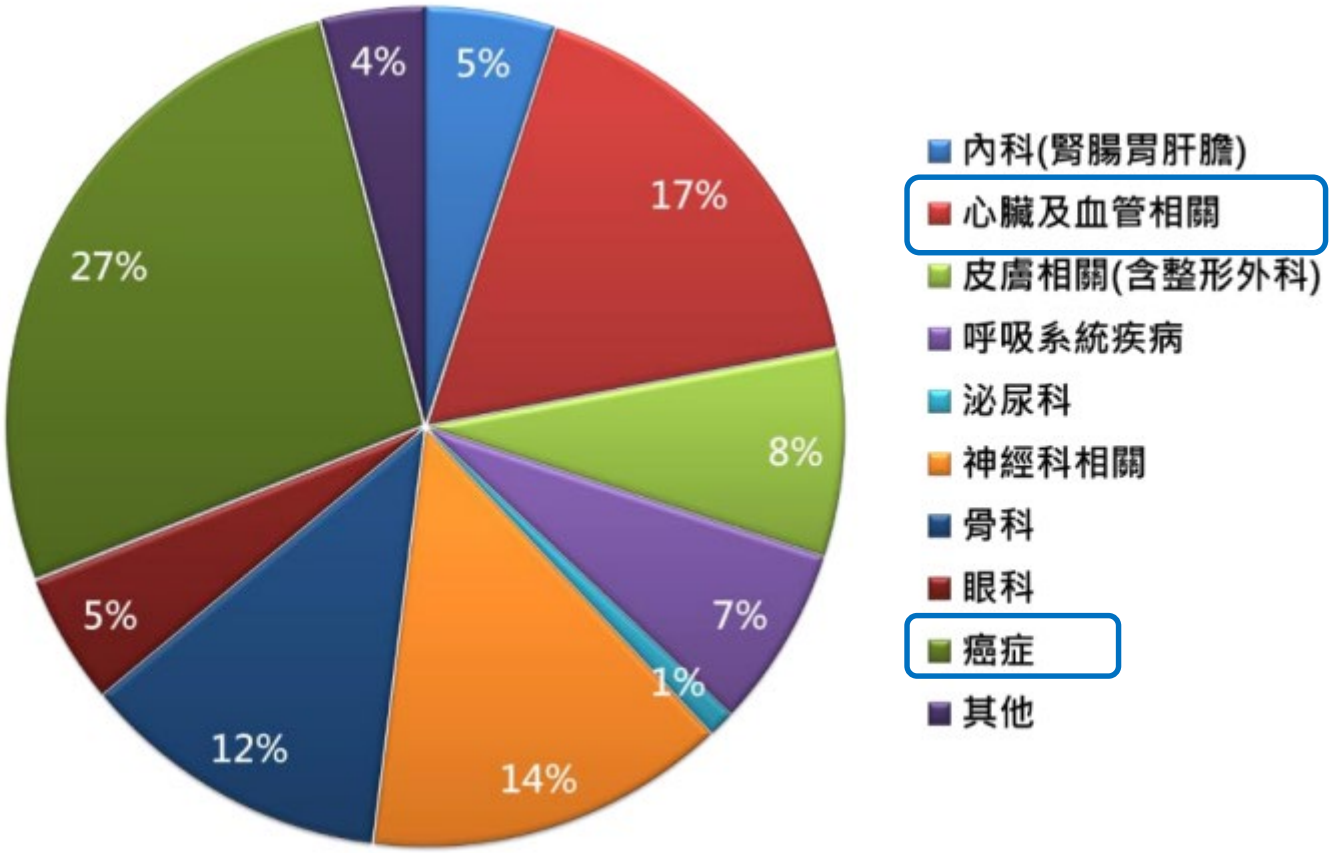
摘自當代醫藥法規月刊
RegMed 2023-07 Vol. 153

2010~2022 年細胞治療製劑臨床試驗之細胞類型



摘自當代醫藥法規月刊
RegMed 2023-07 Vol. 153

2010~2022 年細胞治療製劑臨床試驗治療領域



基因治療製劑

Gene Thearpy

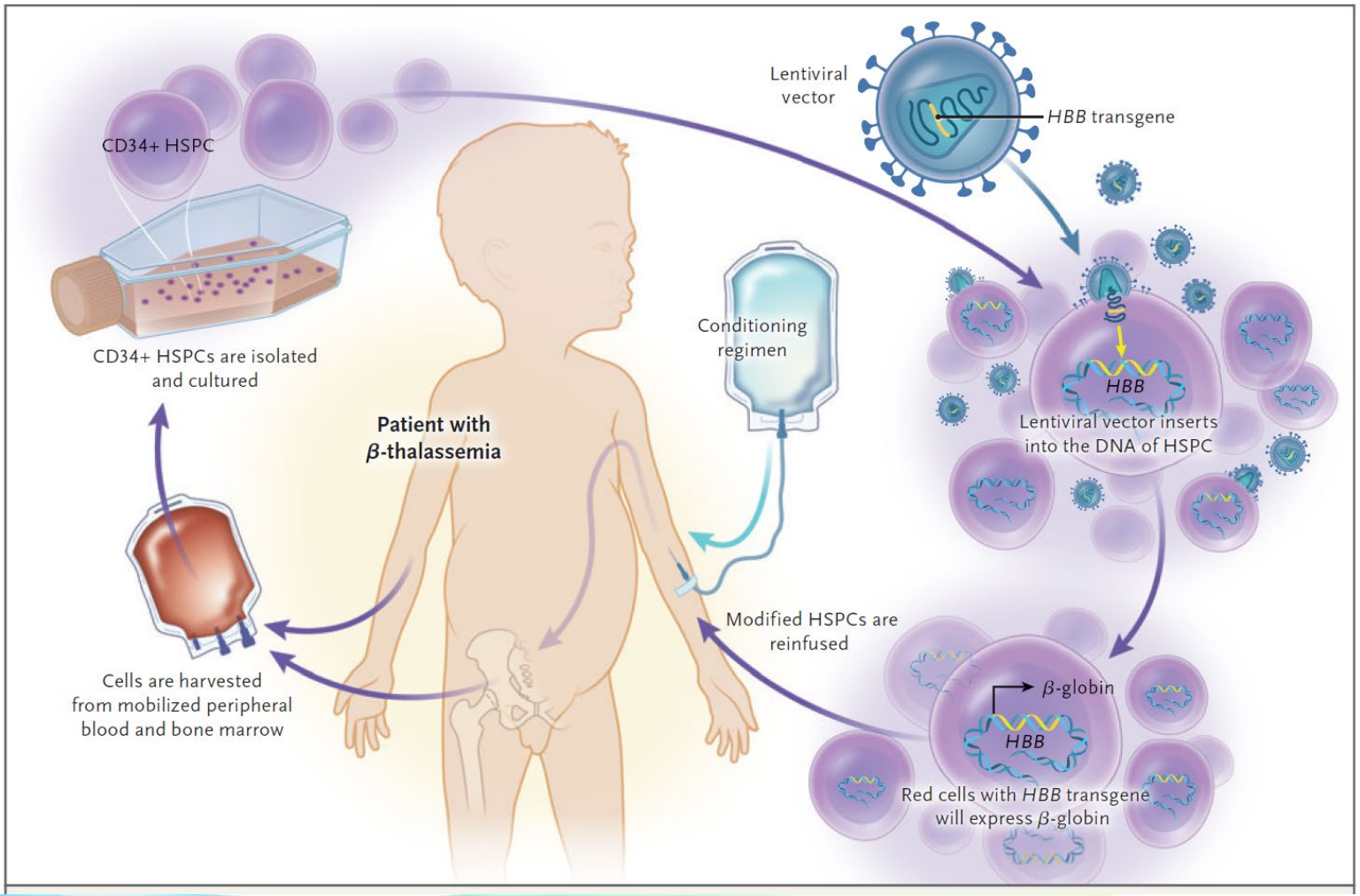
將特定基因(gene)或含特定基因之細胞（gene-modified cells）輸入人體，以達到治療之目的:

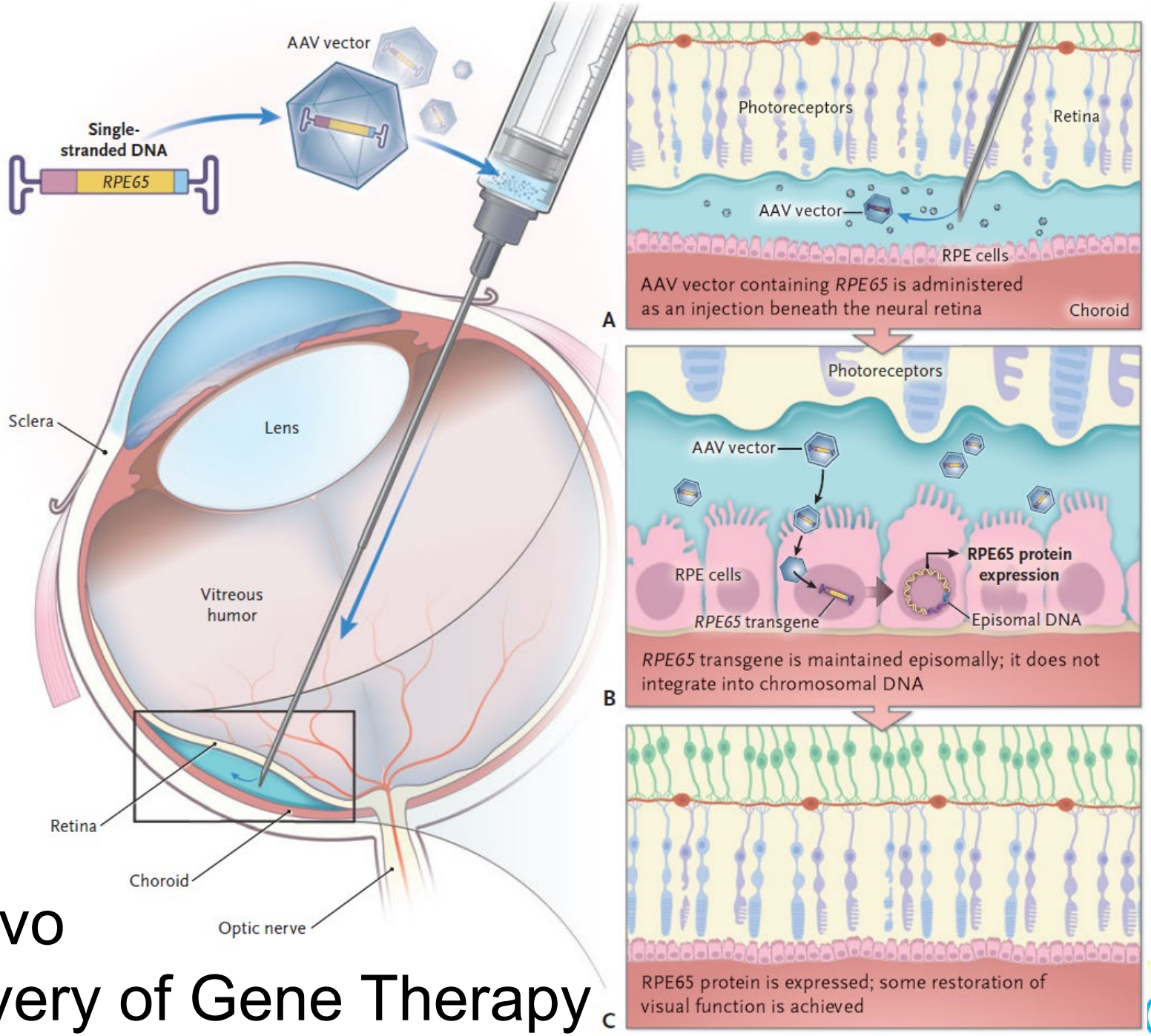
- **Gene Editing:** CRISPR-Cas9 and other gene-editing tools allow for precise modification of a patient's DNA to correct or replace faulty genes.
- **Gene Addition:** Introducing new genes into a patient's cells to compensate for a missing or defective gene.

Methods of Gene Therapy

- integrating vector is introduced into a precursor or stem cell
- gene is delivered in a nonintegrating vector to a long-lived postmitotic or slowly dividing cell
- Ex vivo transduction vs. in vivo transduction

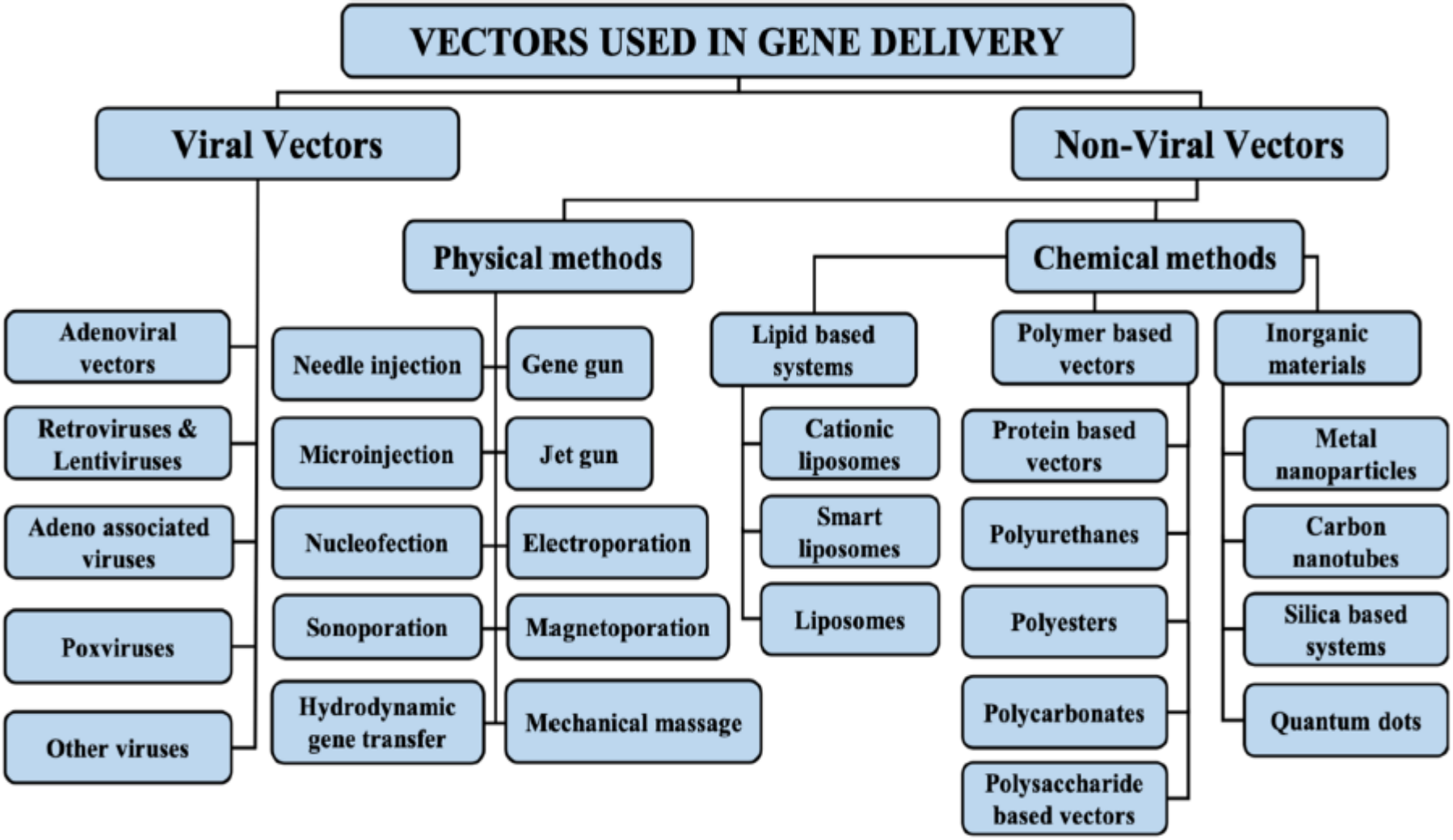
Ex Vivo Delivery of Gene Therapy





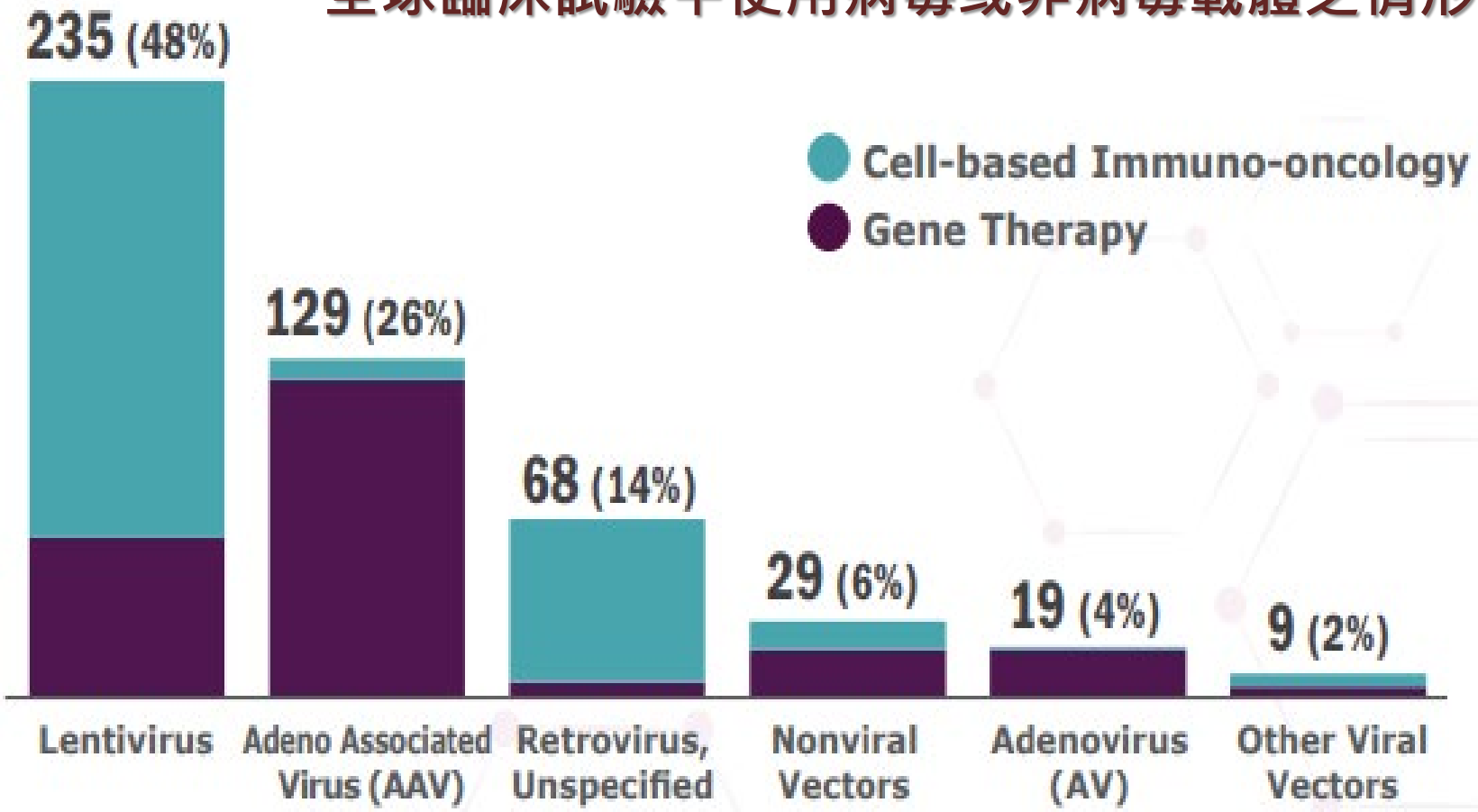
In Vivo Delivery of Gene Therapy

Different Vector Systems



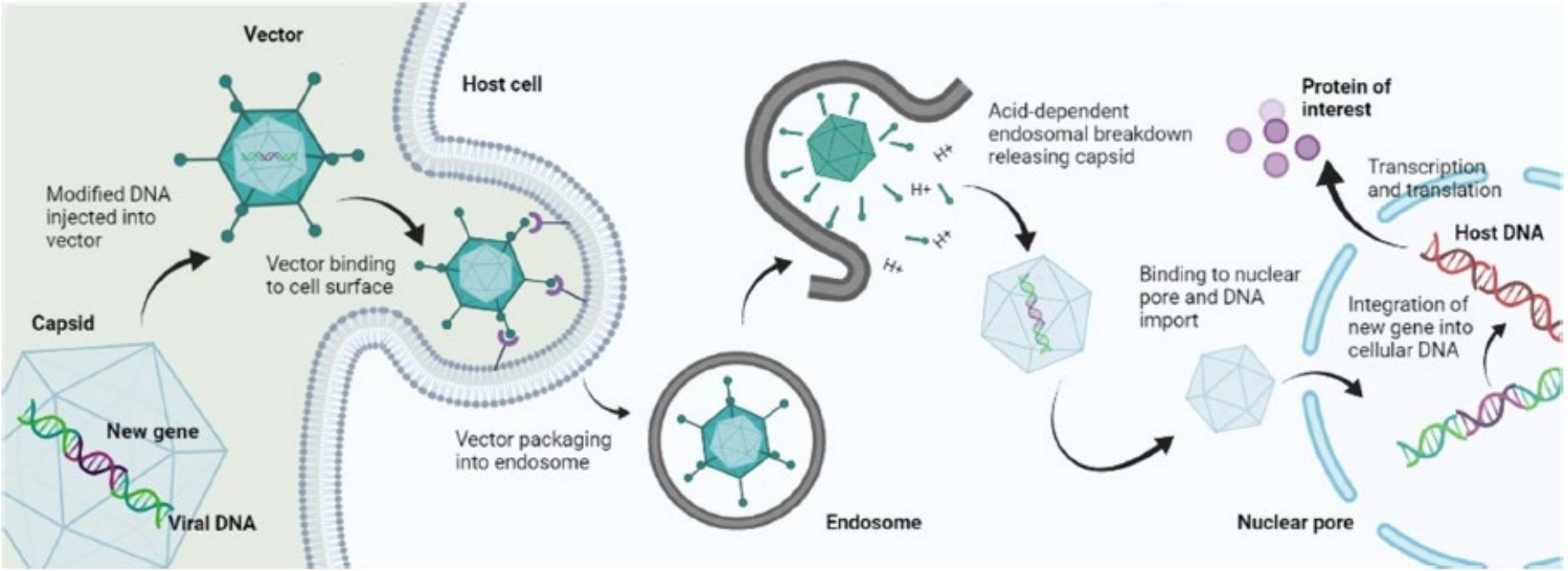
Therapeutic Vectors

全球臨床試驗中使用病毒或非病毒載體之情形



1 Percentages (%) based on trials with known vectors; 604 trials with vector unknown
2 Nonviral vectors include plasmid, transposon, and nanoparticles
3 Other viral vectors include herpes simplex virus (HSV)

Viral Vectors



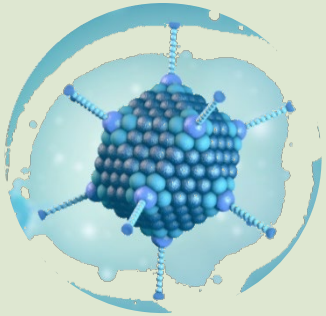
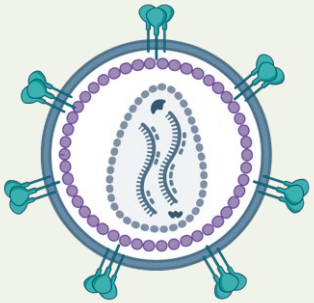
Genes 2022, 13, 1370

Viral Vacters

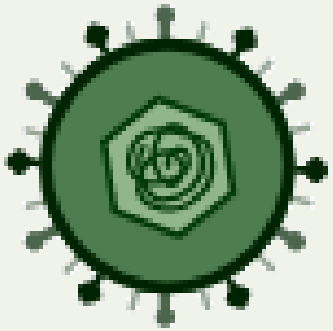
Advantages	Disadvantages
Provide greater gene transfer efficiency in both in vivo and in vitro environments	Can trigger severe immune responses and inflammatory reactions
Persist for longer periods of time in most cases	Their cloning capacity is very limited
Can target a large number of cells	Produced by complex production methods
A large variety of viruses are available to choose from	Low capability of tropism to some specific target cells
Innate ability of tropism toward infection	Can cause mutagenesis by inserting their exogenous DNA into the host genome
Capable of evading endosomes by various mechanisms learned by evolution of viruses	Research is needed to further understand the mechanisms of molecular infection by viruses

Genes 2022, 13, 1370

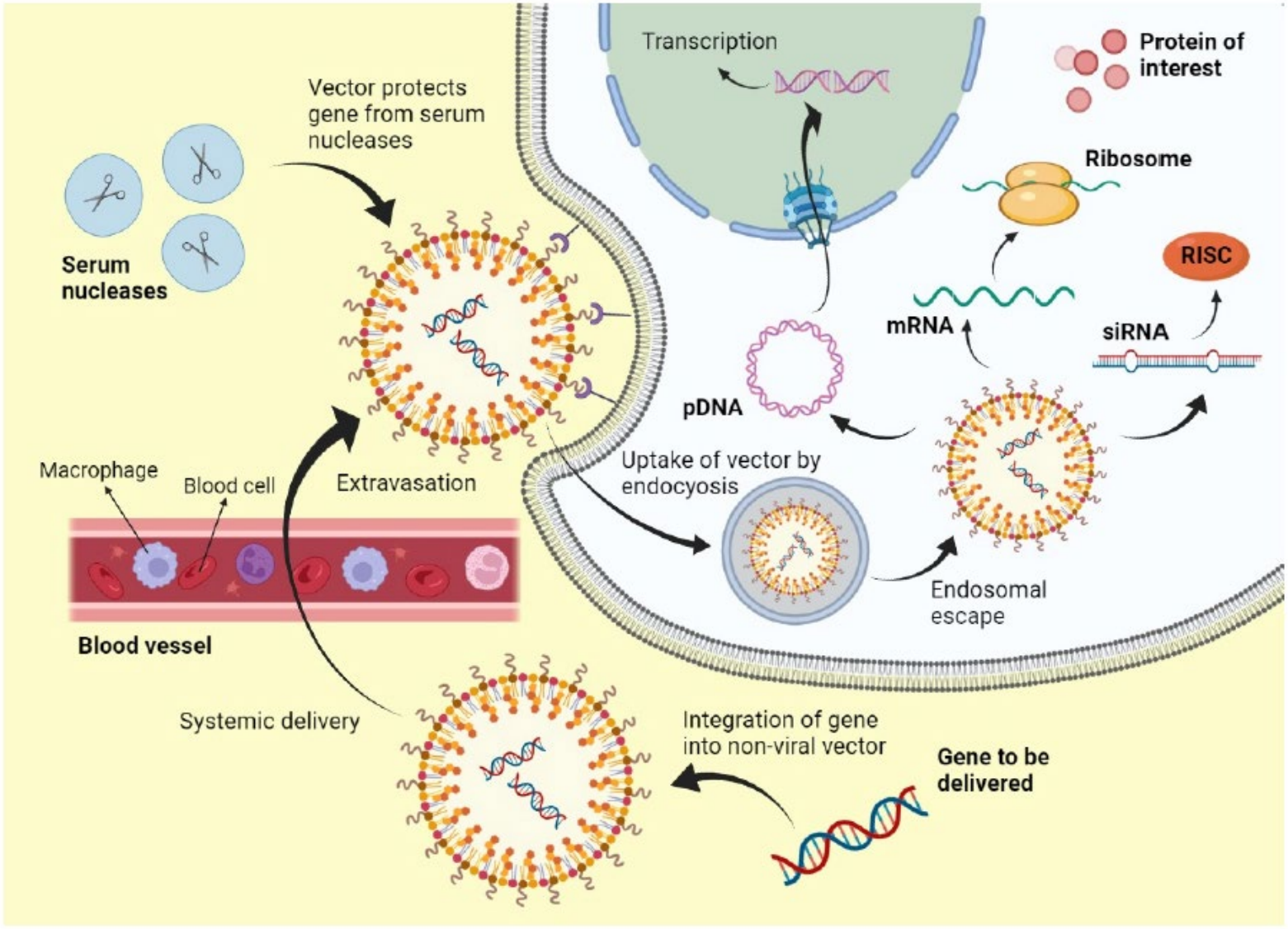
Common Viral Vectors

	Characteristics
Adenoviruses 	• Double-strand DNA (35kb) • Low possibility of integration into the genome of the host cell • severe immune response when systemic use • local administration of transgene
Retroviruses **Lentiviruses** 	• RNA viruses • γ-retrovirus: Integrate to specific host genome → genotoxicity • Lentiviruses: different genomic insertion point → lower extent of mutagenesis • HIV nucleic acid test false positive

Common Viral Vectors

	Characteristics
Adeno-Associated Viruses (AAV) 	• Single strand DNA, nonenveloped, small (5kb) • Low immunogenicity • Do not integrate into host cell genomes → the safest viral vectors
Herpes simplex virus 1 (HSV-1) 	• Double strand DNA, large (152kb) • large capacity of the virus particle (up to 150 Kbp) • Virus DNA will not integrate into host genome • capacity to infect the nervous system

Non-viral Vectors

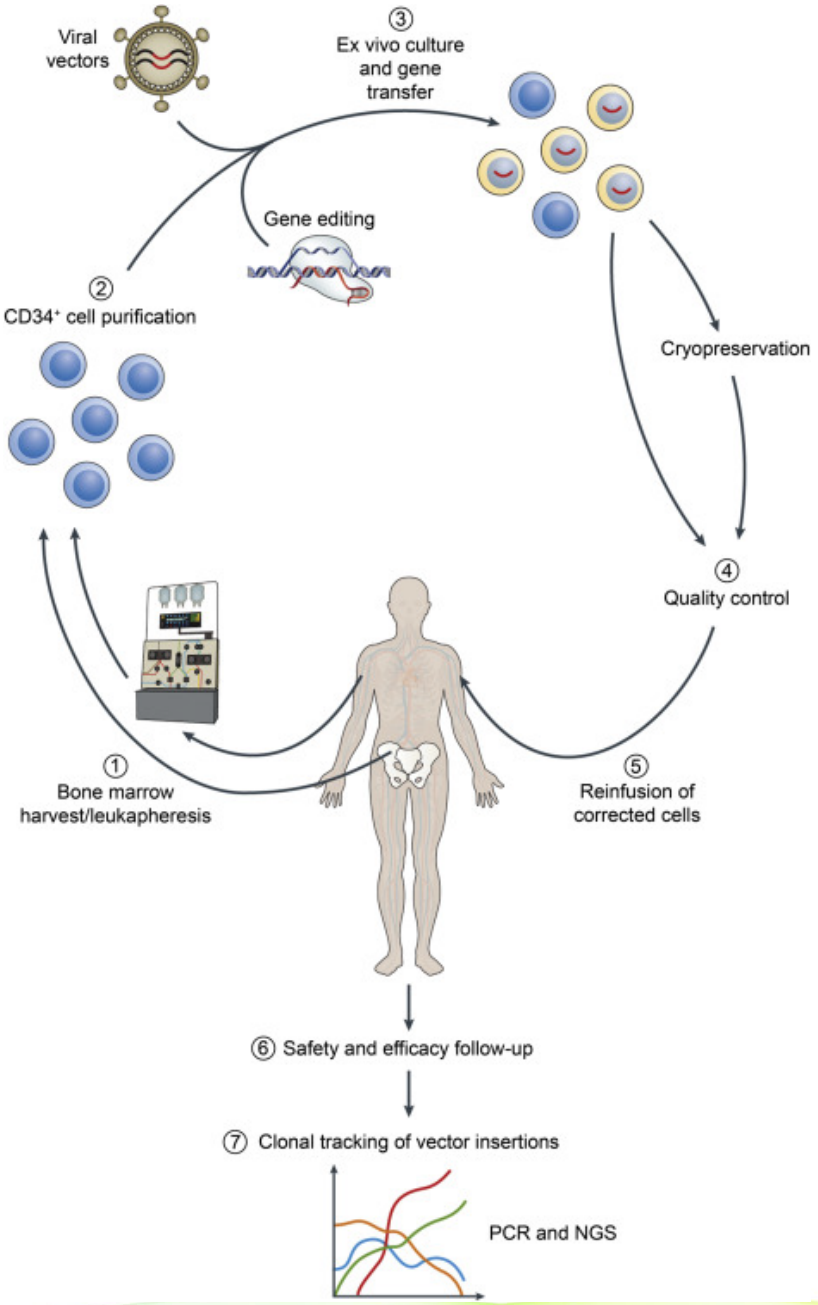


Genes 2022, 13, 1370

- the first ex vivo autologous gene therapy approved by the EMA (2016)
- A HSPC gene therapy
- Indication: treatment of adenosine deaminase (ADA)–deficient severe combined immunodeficiency (SCID)
- Autologous CD34 positive enriched cells transduced with γ-retroviral vector encoding human *ADA* gene

Strimvelis pivotal study

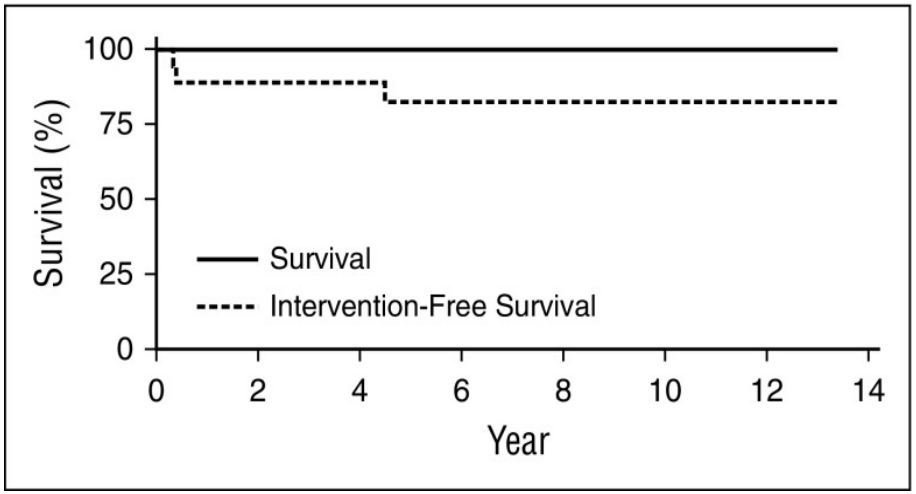
- Single arm, open-label
- 18 patients with ADA-SCID
- HLA-identical family donor was not available and not responding well to ERT
- Busulfan preconditioning



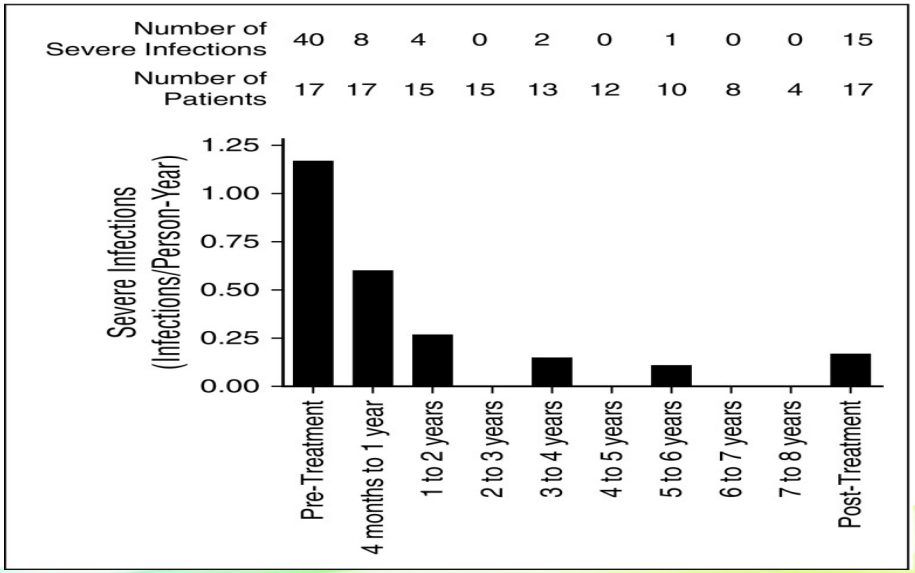
Comprehensive Pharmacology, 2022

Strimvelis pivotal study

- 100% survival, with few patients requiring intervention



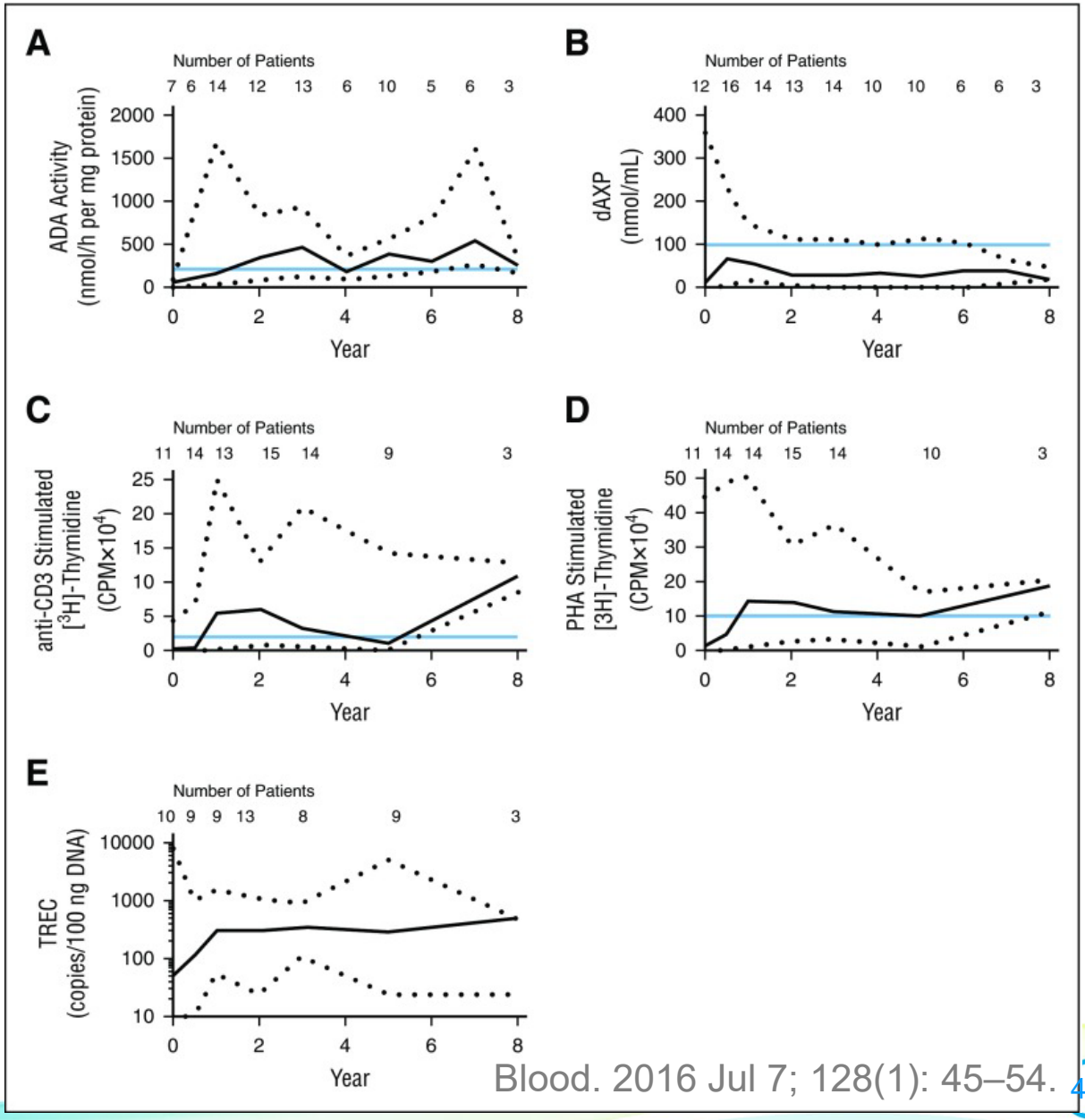
- Immune reconstitution was observed starting 6 months after GT



財團法人醫藥品查驗中心
Center for Drug Evaluation, Taiwan

Blood. 2016 Jul 7; 128(1): 45–54.

- GT supports ADA activity and lymphocyte function



Blood. 2016 Jul 7; 128(1): 45–54.

Pre-transplantation cytoreductive conditioning with low-dose busulfan

- Low-Dose Busulfan Reduces Human CD34+ Cell Doses Required for Engraftment

Withholding of enzyme-replacement therapy

- Favor expansion of the gene-corrected cells

γ-retroviral vector gene therapy expression of *IL2RG* for different form of SCID developed 2nd malignancy (T-cell leukemia)

- safer vectors is needed

zolgensma

- Adeno-associated virus (AAV) vector-based gene therapy
- **Indication**: children <2 years old who have spinal muscular atrophy (SMA) and bi-allelic mutations in the survival motor neuron 1 (SMN1) gene
- SMA:
  - autosomal recessive disorder
  - degeneration of alpha motor neurons in the anterior horn cells of the spinal cord
  - muscle weakness and atrophy.
  - homozygous mutation in the SMN1 gene → survival motor neuron (SMN) protein deficiency

zolgensma

- Adeno-associated virus serotype 9 (AAV-9) vector-based gene therapy
- Vector DNA contains a transgene encoding the human SMN protein
- generalized SMN expression in spinal motor neurons and other cells in the brain, heart, liver, and skeletal muscles
- Single dose IV infusion with $1.1x10^{14}$ vector genomes (vg)/kg
- Pre- and post- infusion: corticosteroid for 30 days then gradually taper

zolgensma

- Phase 3 clinical trial:
  - Single arm, open label, historical control
  - 22 pediatric subjects (mean age 3.9 months; range 0.5 to 5.9 months) with infantile-onset SMA with biallelic SMN1 mutations
  - Endpoint:
    - 13/22 (59%) independent sitting ≥30 sec at 18 m/o vs. 0/23 (0%) in historical control, **p<0.0001**
    - 20/22 (91%) Survival vs. 6/23 (26%) in historical control, p<0.0001
  - Adverse events: vomiting, aminotransferase elevations, acute liver injury, thrombocytopenia, and increases in troponin I levels.

Lancet Neurol 2021 Apr;20(4):284-293

zolgensma

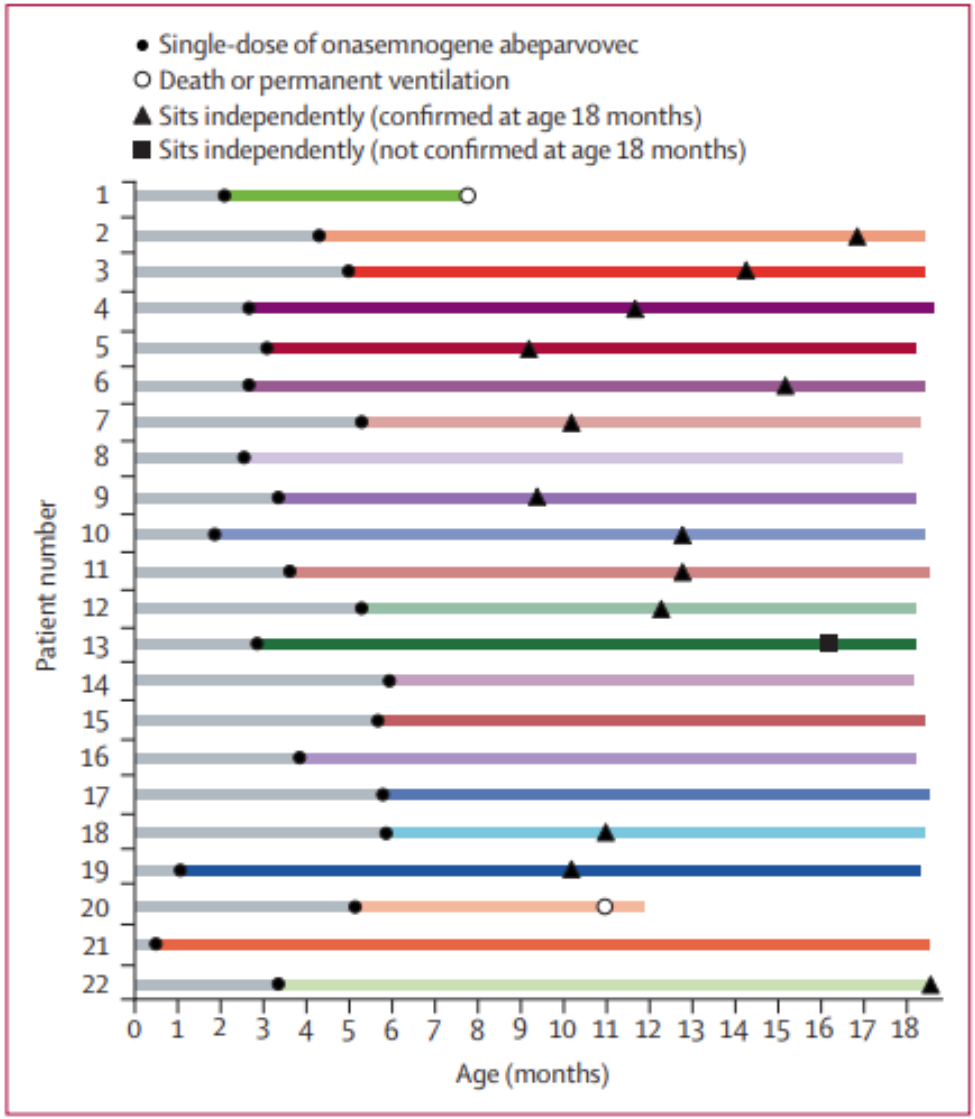
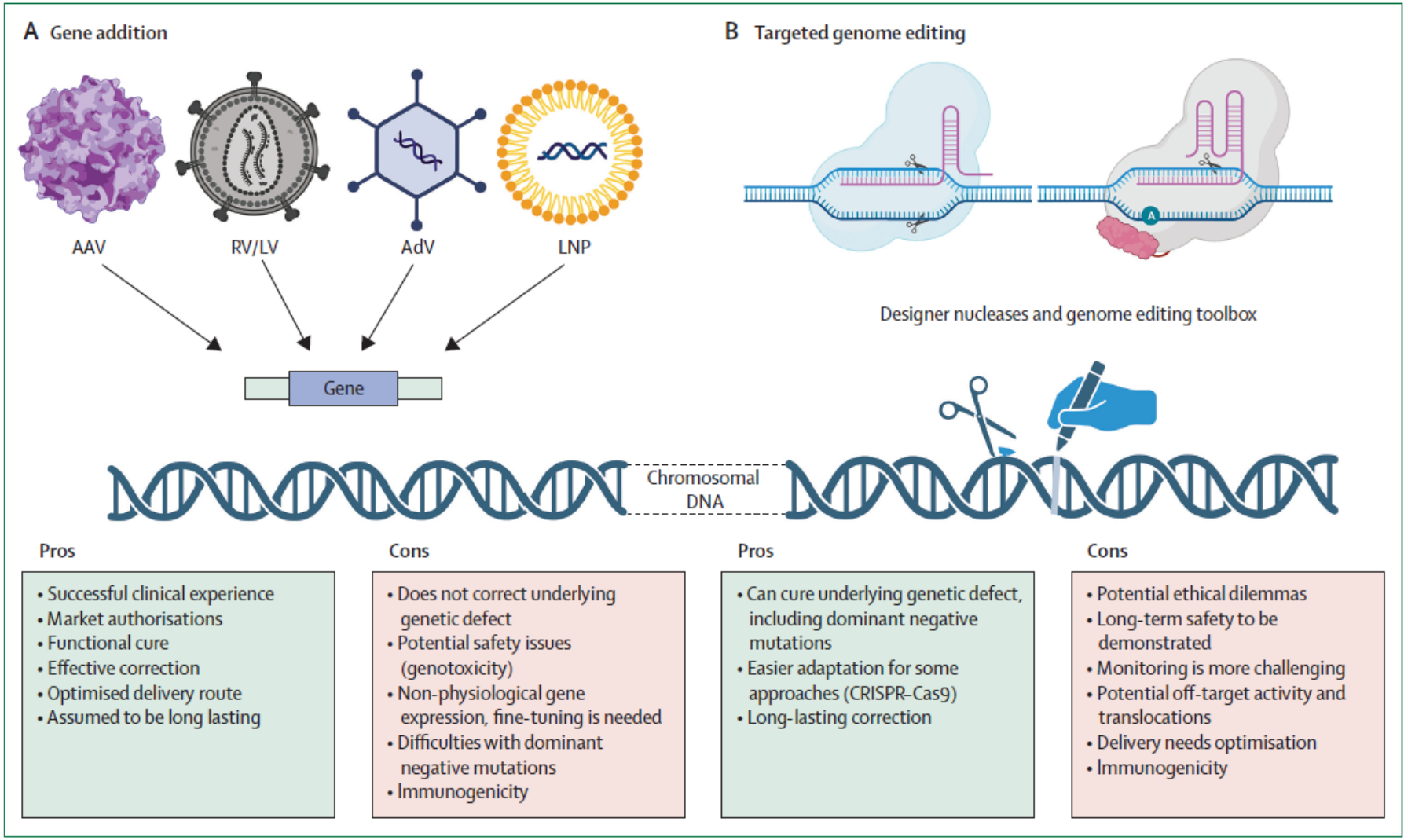


Figure 2: **Survival at age 18 months and independent sitting at age 14 months (coprimary endpoints)**

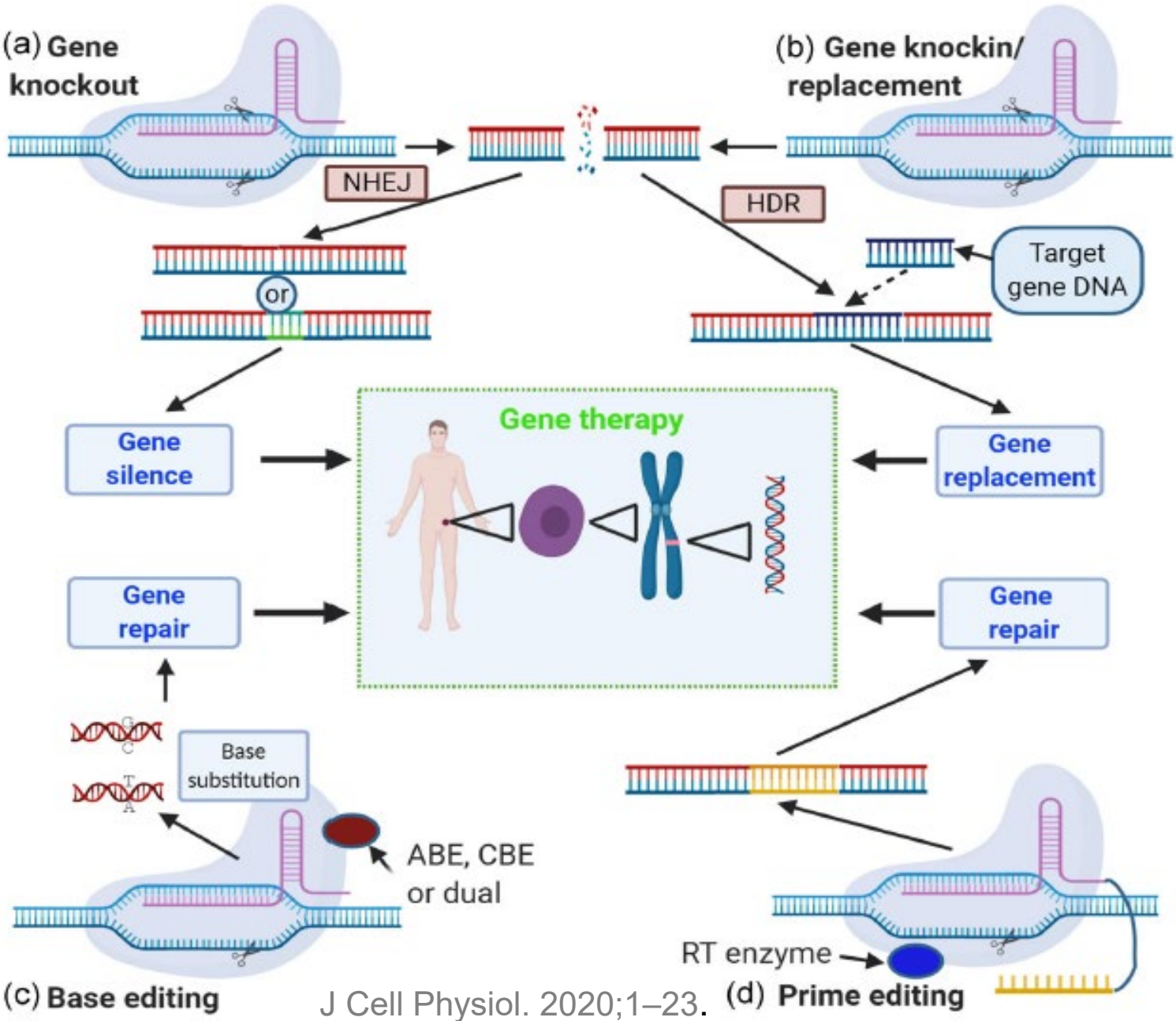
Lancet Neurol 2021 Apr;20(4):284-293

Gene addition approaches vs. Targeted genome editing approaches



The Lancet November 22, 2023

CRISPR/Cas9



J Cell Physiol. 2020;1–23.

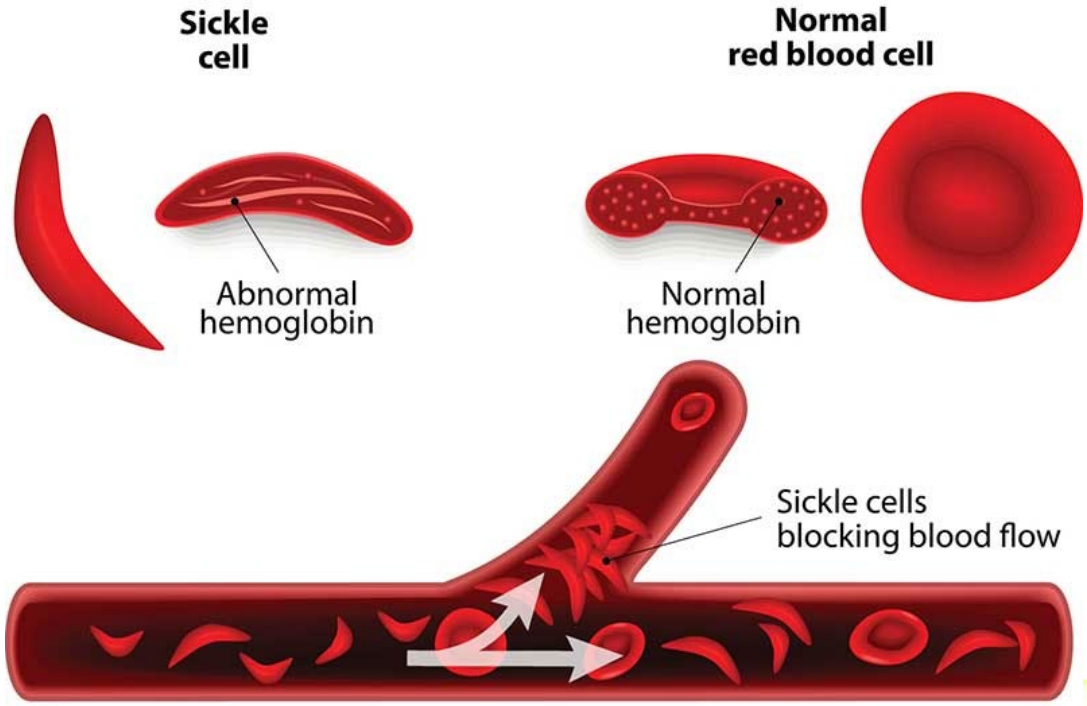
casgevy™
(exagamglogene autotemcel)
suspension for IV infusion

- Indication: **Sickle cell disease**
- Inherited red blood cell disorder :

  β-globin gene (HBB) on chromosome 11

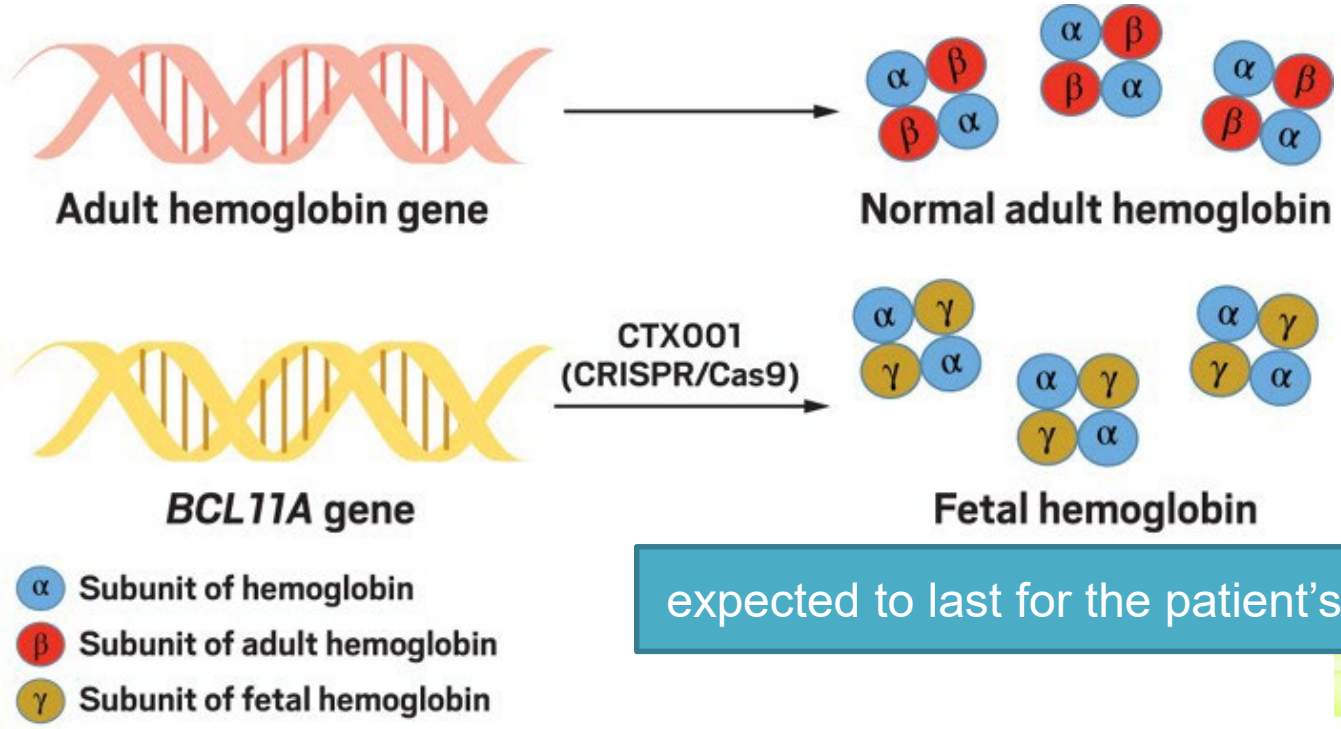
- Pain, anemia, swelling in the hands and feet, infections, stroke
- Treatment:

  bone marrow transplantation



casgevy™
(exagamglogene autotemcel)
suspension for IV infusion

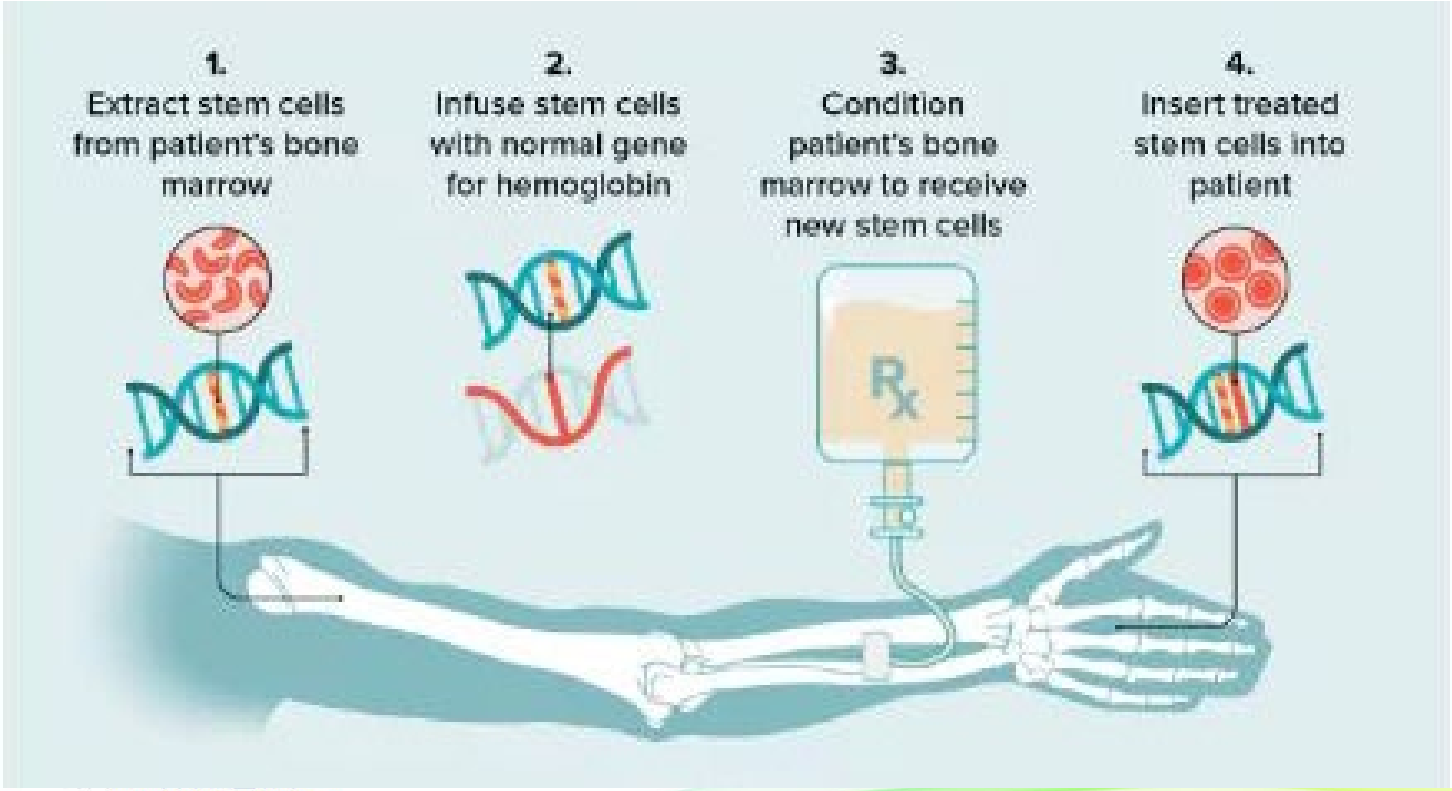
- Autologous cell-based gene therapy product
- Edit at the GATA1 binding site of the BLC11A gene
- SPY101 single guide RNA (sgRNA) → Cas9 to make a DNA double stranded break in the GATA1 transcription factor binding site → **insertions and deletions (indels)** → reduce BCL11A expression →**increased HbF production**



expected to last for the patient's lifetime

casgevy™
(exagamglogene autotemcel)
suspension for IV infusion

- single exa-cel dose of ≥3x10^6 CD34+ cells/kg administered intravenously (IV)
- after full myeloablative conditioning with busulfan

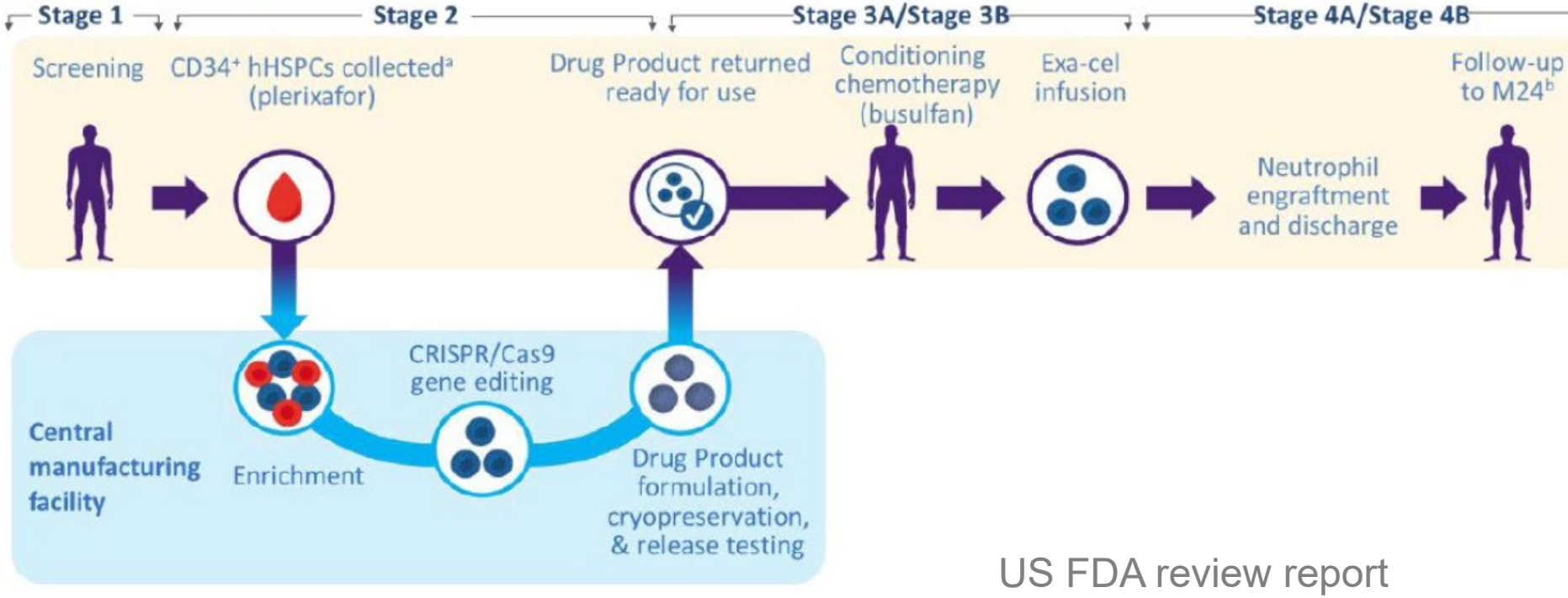


Center for Drug Evaluation,Taiwan

casgevy™
(exagamglogene autotemcel)
suspension for IV infusion

- Study 121: a single-arm, uncontrolled study in adult and adolescent patients with SCD (N=14)

Figure 1. Design of Study 121



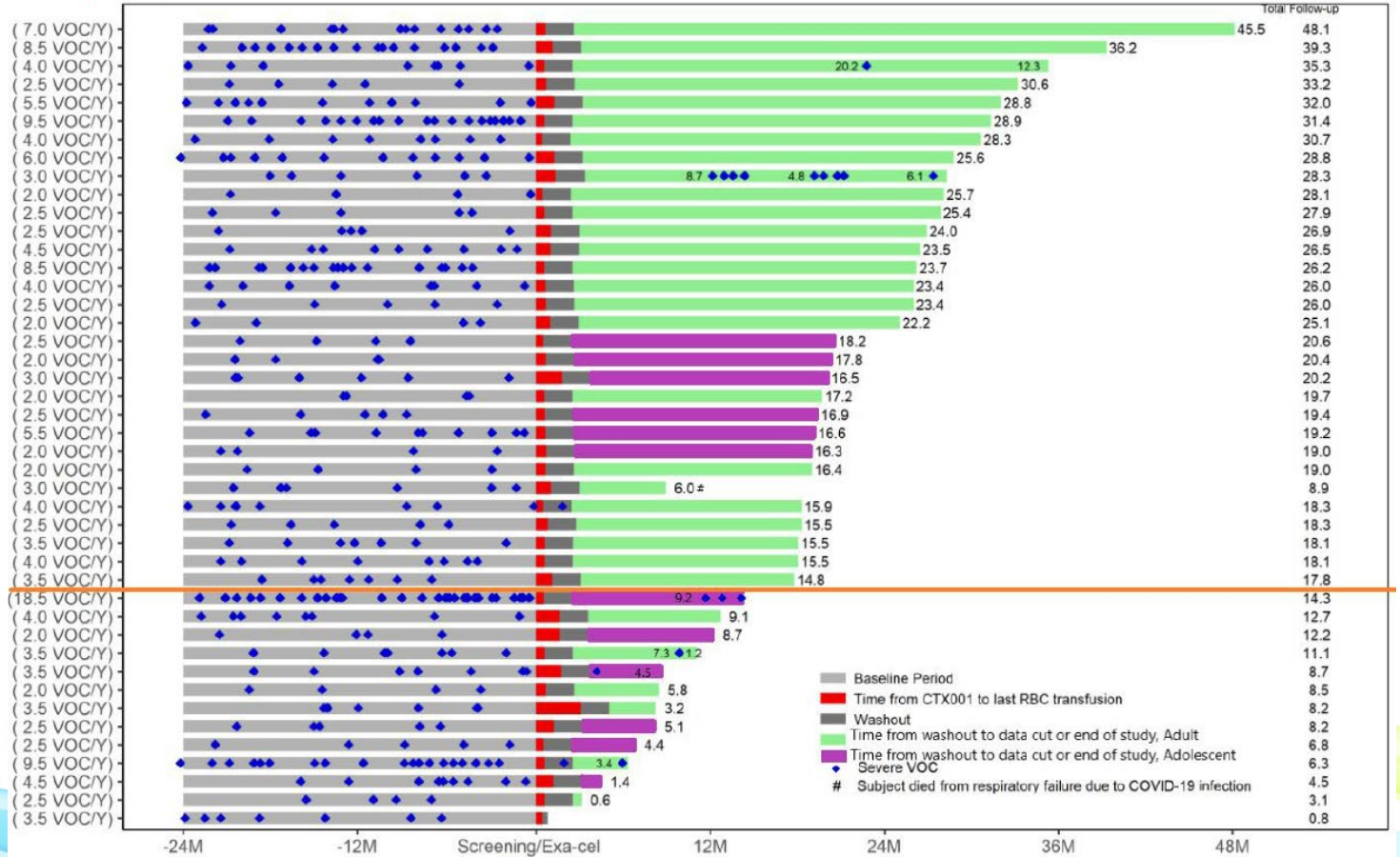
US FDA review report

casgevy™
(exagamglogene autotemcel)
suspension for IV infusion

US FDA review report

- Study 121 efficacy:
  - **29/30** Absence of vaso-occlusive crises (VOCs) for≧12 months
  - 28/30 remained free of VOCs for a mean duration of 22.3 months

Figure 3. Historical and Post Exa-cel VOCs and sVOC-Free Duration in All Dosed Subjects, Study 121, FAS N=44



Safety of Gene Therapy

- 輸注相關不良反應/細胞激素釋放
  - Use of adjuvant immunomodulatory drugs
- 感染/發炎反應
  - 具複製能力的病毒，
  - 當共同感染細胞或製品汙染，可能產生vector與wild type virus重組
  - 病毒潛伏(Latency): 病毒在活化的風險，如herpesvirus
- 過度表現
  - 轉殖基因過度表現凝血因子
- 脫靶效應
  - Genome editing activity with off-target effects
  - 可能造成惡性腫瘤風險、或是影響其他正常基因功能
- 惡性腫瘤風險
  - Insertional mutagenesis: vector inserts into the DNA of a cell and disrupts a gene
  - Genome editing activity
  - Prolong expression of transgene encodes growth factors, cell division proteins (eg. p53)
  - Immunosuppression

一般建議追蹤15年

Figure 1. Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events

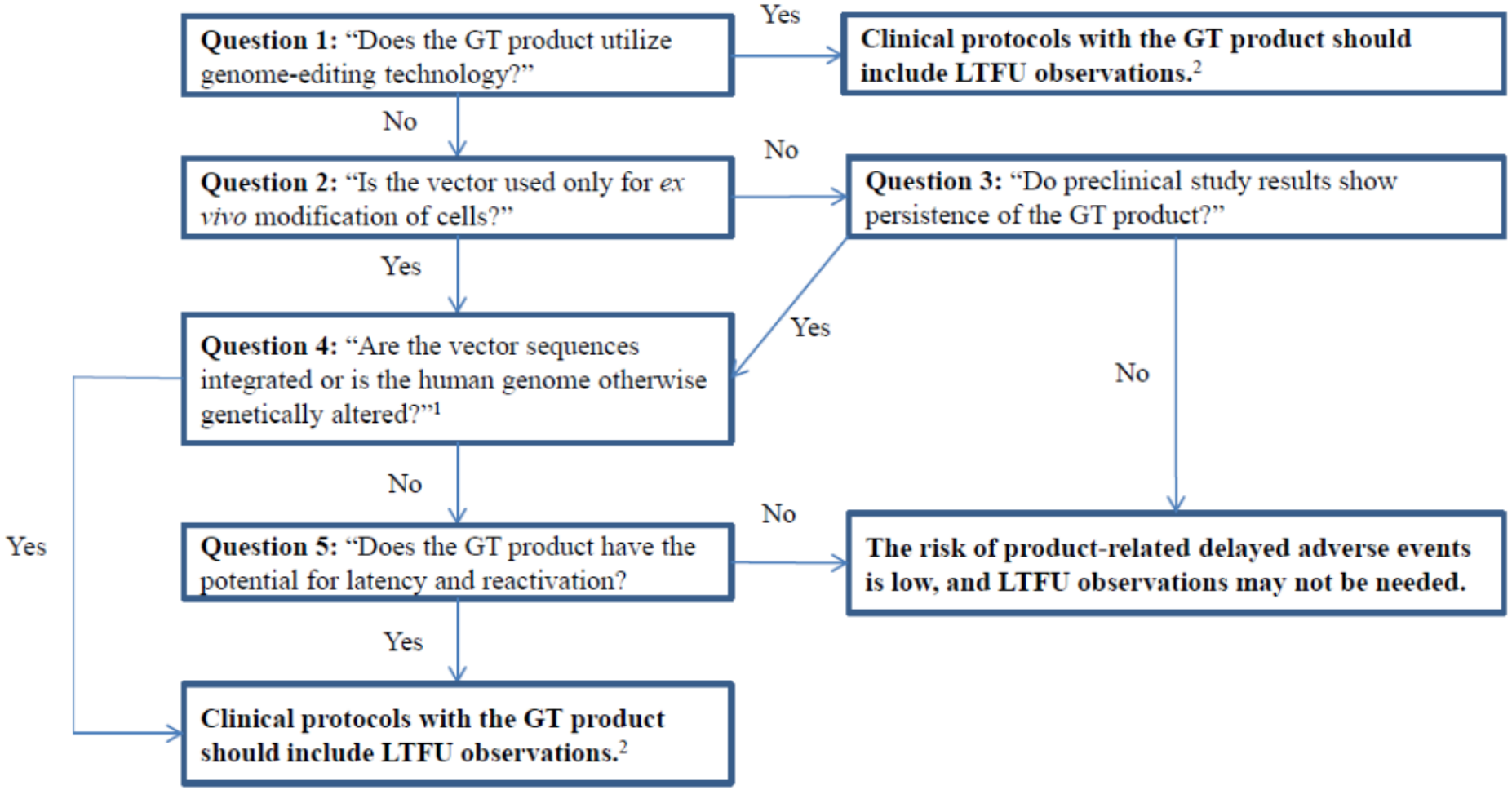


Table 1. Propensity of Commonly Used Gene Therapy Products/Vectors to Modify the Host Genome

Product/Vector Type	Propensity to Modify Genome[1]	Long Term Follow-up Observations[2]
Plasmid	No	No
RNA	No	No
Poxvirus	No	No
Adenovirus	No	No
Adeno-associated virus[3]	No	Product specific
Herpesvirus	No, but may undergo latency/reactivation	Yes
Gammaretrovirus	Yes	Yes
Lentivirus	Yes	Yes
Transposon elements	Yes	Product specific
Microbial vectors for gene therapy (MVGT)[4]	No, but may persist and undergo reactivation	Product specific
Genome editing products	Yes; permanent changes to the host genome	Yes

CAR-T製劑

CAR-T製劑

- CAR-T為經過基因修飾的免疫細胞療法
- 截至2023年5月，國內外核准的CAR-T產品

	Kymriah	Yescarta	Tecartus	Breyanzi	Abecama	Carvykti
標的	CD-19	CD-19	CD-19	CD-19	BCMA	BCMA
US FDA						

- 目前核准適應症均為血液惡性腫瘤
- CAR-T尚屬於新興的治療領域，其長期安全性資料仍在累積中，對於CAR-T治療後的長期安全性追蹤，目前國內外尚未有共識。

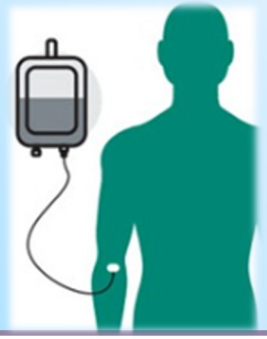
CAR-T製劑適應症

	Kymriah	Yescarta	Tecartus	Breyanzi	Abecama	Carvykti
標的	CD-19	CD-19	CD-19	CD-19	BCMA	BCMA

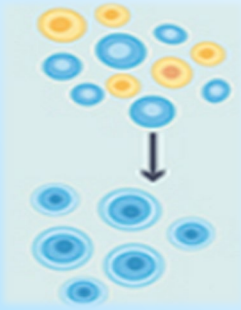
- 以CD-19為抗原標的CAR-T治療，核准適應症主要為**B細胞淋巴瘤以及B細胞急性骨髓性白血病**
  - 如瀰漫性大B細胞淋巴瘤、被套細胞淋巴瘤與濾泡細胞淋巴瘤等
- 以BCMA為抗原標的CAR-T治療，核准適應症主要為**多發性骨髓瘤**。
- 病人通常需要在CAR-T治療前先執行淋巴排空(lymphodepletion)清除性化療。

CAR-T的製備及施用

收集病人周邊血

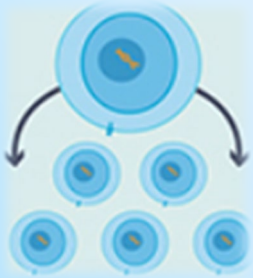


分離並活化T cell

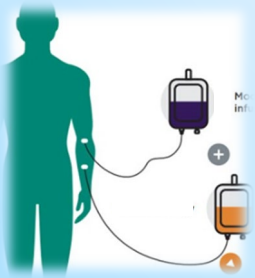


利用載體導入
CAR基因片段

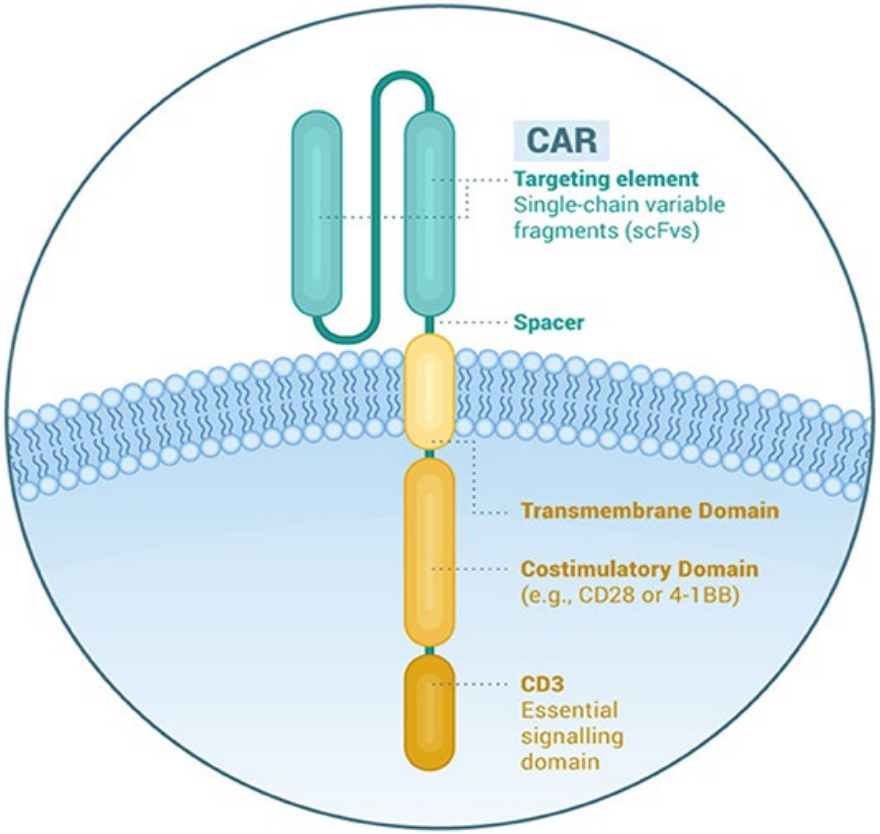
體外增殖
CAR-T cell



回輸CAR-T cell
清除性化療



CAR-T的結構特色



2.2.1細胞外抗原結合部位

- single chain variable fragment辨認腫瘤細胞外目標抗原

2.2.2 連接部位

- 提供CAR足夠的彈性

2.2.3 跨膜部位

2.2.4 細胞內訊息傳遞部位

- 第二代CAR除了CD3ζ之外，同時具備細胞內共同刺激區域

Rodríguez-Lobato, Front. Oncol., 28 July 2020

CAR-T治療的急性風險

急性不良反應通常會於治療後的第一個月內發生

1.細胞激素釋放症候群

- 使用tocilizumab和其他免疫抑制藥物如類固醇來治療

2.免疫作用細胞相關之神經毒性

- 使用類固醇治療急性神經學毒性

3.急性感染

4.淋巴排空清除性化療導致的血球降低

CAR-T治療的長期風險

長期風險：治療後90天以上出現或是仍持續的風險

B細胞耗竭(B cell depletion)

- CD-19或BCMA為抗原標的之常見風險
- B細胞耗竭導致免疫球蛋白低下
- 發生率25-38%，可能持續數年
- 可能導致疫苗注射效果不佳
- 大多數的B細胞耗竭和免疫球蛋白低下都會在六到八個月之後，因為CAR-T 細胞的消失而恢復

CAR-T治療的長期風險

血球減少(cytopenia)

- 臨床表現包括貧血、血小板減少、嗜中性球白血球低下
- 血球減少為CAR-T治療後常見的短期風險，但仍有可能出現持續三個月以上的慢性血球減少
- 嚴重慢性血球減少的發生率16%，持續15-22個月
- 高風險族群
  - CAR-T治療後發生顯著急性細胞激素釋放症候群的病人
  - 先前接受過較多線治療的病人
  - CAR-T治療與造血幹細胞移植期間短於一年的病人
- 尚未觀察到CAR-T治療後進展至骨髓造血不良(MDS)

CAR-T治療的長期風險

感染

- CAR-T治療的第一個月內，感染的機率最高；治療後30-120天之間，感染的機率下降 (發生率14-31%)
- 長期感染以病毒感染風險較高
- 僅有少部分病人為嚴重感染

續發性癌症

- 尚未有足夠的證據顯示已上市的CAR-T治療後發生續發性癌症的風險
- 研究追蹤時間的中位數介於14.9~61個月。尚待更長期的結果
- 不同基因導入方式的風險不同：使用PiggyBac跳躍子進行基因片段導入的CAR-T，曾在早期臨床試驗中發生表現嵌入基因的惡性T細胞淋巴瘤案例

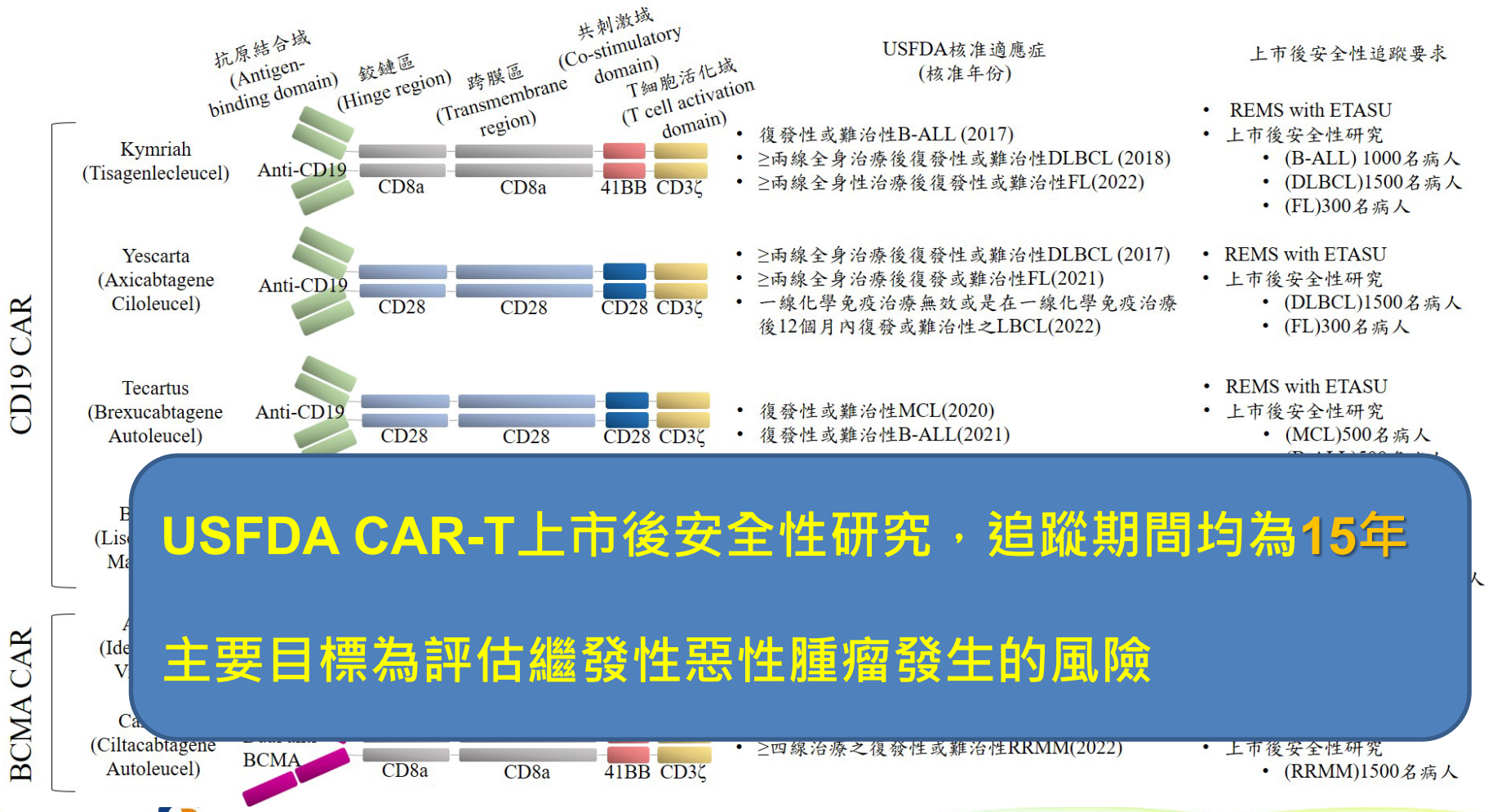
CAR-T治療的長期風險

脫腫瘤毒性(off-tumor toxicity)及脫靶毒性(off-target toxicity)

- Off-tumor toxicity：人體組織中其餘細胞也可能會表現CAR標的之相關抗原，因此可能造成毒殺腫瘤細胞之外的毒性
- Off-target toxicity：CAR-T細胞表面受體與其他交叉反應抗原(cross-reactive antigens)間產生脫靶效應
- 神經性毒性：
  - **急性腦水腫**(罕見)：腦部周細胞(pericyte)表現CD-19造成off-tumor toxicity
  - **慢性類似金森氏症**(parkinsonism)漸進性運動障礙：腦部基底核(basal ganglia)中神經元與星狀細胞(astrocyte)發生慢性脫腫瘤/脫靶毒性

- 針對CD-19或是BCMA標的之CAR-T產品專一性較佳。若產品針對新的CAR標的，或是針對實體腫瘤的CAR-T治療，這類的脫靶毒性及脫腫瘤毒性更需要特別注意

已上市CAR-T產品的安全性追蹤要求



USFDA CAR-T上市後安全性研究，追蹤期間均為15年

主要目標為評估繼發性惡性腫瘤發生的風險

財團法人醫藥品查驗中心
Center for Drug Evaluation, Taiwan

Cappell, K. M. Nature Reviews Clinical Oncology 1-13 (2023).
Boettcher, M. Journal of Clinical Medicine, 11(8) (2022)

細胞治療製劑

細胞治療特色?

風險分析概念

風險分析概念 最小操作

最小操作 (Minimal Manipulation)

對於人類細胞治療產品的細胞製造或操作過程，不經體外細胞培養程序，且操作過程不改變細胞原有的生物特性，稱為最小操作（Minimal manipulation）。

裁切（cutting）、研磨（grinding）、塑型（shaping）、離心（centrifugation）、細胞分離（cell separation）、濃縮（concentration）或純化（purification）、選擇性移除週邊血之 B 細胞、T 細胞、癌細胞（malignant cells）、紅血球（red blood cells）或血小板（platelets）、浸潤於抗生素或抗菌液（soaking in antibiotic or antimicrobial solutions）、滅菌（sterilization）、輻射照射（irradiation）、過濾（filtering）、冷凍乾燥（lyophilization）、冷凍（freezing）、冷凍保存（cryopreservation）等操作程序仍屬於最小操作範圍。

風險分析概念 同源使用

同源使用 (Homologous Use)

捐贈者的細胞或組織物用來修護（repair）、重建（reconstruction）、替代（replacement）或補充（supplementation）受試者的細胞或組織物，而該細胞或組織物用在受試者的功能與捐贈者相同者稱之。

細胞治療整體考量

- Prolonged biologic activity after a single administration
- Immunogenicity
- Invasive procedure
- Dynamic nature of living cells (may differentiate in vivo into undesired cell types)、ability to migrate、pre-treatment (donor or recipient)
- Feasibility of manufacturing
- Preclinical data may not always be as informative as for small molecule pharmaceuticals

臨床前試驗設計可參考下述指引

- 人類自體細胞治療產品研發 - 臨床前安全性資料及人體試驗起始劑量.當代醫藥法規月刊(2015-12) http://www.cde.org.tw/Content/Files/Knowledge/5e5e0172-460b-43dd-85ad-d30e1eb506cb.pdf
- US FDA: Preclinical Assessment of Investigational Cellular and Gene Therapy Products November 2013

Case: MACI®

	MACI® Autologous Cultured Chondrocytes on a Porcine Collagen Membrane
Indication	MACI (autologous cultured chondrocytes on porcine collagen membrane) is an autologous cellularized scaffold product indicated for the repair of single or multiple **symptomatic, full-thickness cartilage defects of the knee** with or without bone involvement in adults. Limitations of Use: Effectiveness of MACI in joints other than the knee has not been established. Safety and effectiveness of MACI in patients over the age of 55 years have not been established.
Dosage	• The amount of MACI implanted depends on the size (surface area in cm^2) of the cartilage defect. The surgeon should trim the MACI implant to the size and shape of the defect, to ensure the damaged area is completely covered. •Dosage forms and strengths: MACI implant is available as a cellular sheet, 3 x 5 cm, with a 0.5-cm^2 section removed from the lower left-hand corner, consisting of autologous cultured chondrocytes on a resorbable Type I/III collagen membrane at a density of at least 500,000 cells per cm^2

From US FDA MACI® assessment report

Cartilage defects

- Cause:
  Often caused by traumatic injury, disrupt the normal anatomic relationship of cartilaginous surfaces between articulating joints

- Symptom:
  severe pain, knee swelling, and reduction in mobility that affects quality of life

- Arthroscopic microfracture is a common procedure performed in the US for treatment of symptomatic knee cartilage defects, where the defect is debrided and small holes are drilled into the subchondral bone to allow bleeding into the defect site. Stromal cells then effect a repair by producing a scar type tissue called fibrocartilage, which lacks the biomechanical properties of articular cartilage, but does provide an improvement in symptoms

From US FDA MACI® assessment report

MACI® clinical studies

	Study design	Treatment group	Study population	Primary endpoint
SUMMIT study (phase III)	MC, RD, OL, 2 year, N=144	• MACI • Microfracture	18~55 y/o, with at least 1 symptomatic Outerbridge Grade III or IV focal cartilage defect	co-primary efficacy endpoints: change from baseline to Week 104 for Knee injury and Osteoarthritis Outcome Score (KOOS) in two subscales: Pain and Function
SUMMIT study (Extension)	3 year , N=128	No treatment	Pt complete phase III study	

MC, multicenter; RD, randomized; OL, open label

MACI® SUMMIT study

- Study population
  - 18 and 55 years (inclusive), with at least 1 symptomatic Outerbridge Grade III or IV focal cartilage defect on the medial femoral condyle, lateral femoral condyle, and/or trochlea (defect size equal to or greater than 3.0 cm^2 irrespective of location).
  - Patients with osteoarthritis in the target knee joint (Kellgren-Lawrence Grade 3 or 4) were excluded.

From US FDA MACI® statistical assessment report

MACI® SUMMIT study

- Co-primary efficacy variables
  - Changes from Baseline to Week 104 for the patient's KOOS Pain and Function (Sports and Recreational Activities [SRA]) scores

    (superiority)

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Source: Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998 Aug;28(2):88-96.

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a questionnaire designed to assess short and long-term patient-relevant outcomes following knee injury. The KOOS is self-administered and assesses five outcomes: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life. The KOOS meets basic criteria of outcome measures and can be used to evaluate the course of knee injury and treatment outcome. KOOS is patient-administered, the format is user-friendly and it takes about 10 minutes to fill out.

Scoring instructions

The KOOS's five patient-relevant dimensions are scored separately: Pain (nine items); Symptoms (seven items); ADL Function (17 items); Sport and Recreation Function (five items); Quality of Life (four items). A Likert scale is used and all items have five possible answer options scored from 0 (No problems) to 4 (Extreme problems) and each of the five scores is calculated as the sum of the items included.

Interpretation of scores

Scores are transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems as common in orthopaedic scales and generic measures. Scores between 0 and 100 represent the percentage of total possible score achieved.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Pain

P1 How often is your knee painful?	☐ Never	☐ Monthly	☐ Weekly	☐ Daily	☐ Always

What degree of pain have you experienced the last week when…?

P2 Twisting/pivoting on your knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P3 Straightening knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P4 Bending knee fully	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P5 Walking on flat surface	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P6 Going up or down stairs	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P7 At night while in bed	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P8 Sitting or lying	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P9 Standing upright	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Sport and recreation function

What difficulty have you experienced the last week…?

Sp1 Squatting	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp2 Running	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp3 Jumping	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp4 Turning/twisting on your injured knee	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Sp5 Kneeling	☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

MACI® SUMMIT study results

- The demographic characteristics of subjects in the SUMMIT study were similar in both treatment groups.
  - The majority of subjects were male
    62% MACI, 67% microfracture
  - The mean age was 35 (MACI) and 33 (microfracture) years.

- The target defects were similar between the 2 treatment groups at Baseline.
  - the index lesion was most frequently located in the medial femoral condyle (75.0% MACI and 73.6% microfracture)
  - the median size of the index lesion and the median total defect size surface area were similar for both treatment groups (4.0 cm^2 and 4.5 cm^2, respectively).
  - prior orthopedic knee surgeries had been performed on the index knee for 40.3% of MACI and 43.1% of microfracture patients.
- The level of sports activity with physical strain on the knee prior to the onset of symptoms was higher for patients in the microfracture group as compared to the MACI group.
  - Sports activity was rated as highly competitive in 17 patients (23.6%) in the MACI group and 27 patients (37.5%) in the microfracture group.

MACI® SUMMIT study - results

Primary Efficacy endpoints

Table 2: Changes from Baseline to Week 104 in KOOS Pain and KOOS Function scores

	MACI Mean (SD)			Microfracture Mean (SD)		
	N	Pain	Function	N	Pain	Function
Baseline	72	37.0 (13.5)	14.9 (14.7)	71	35.4 (12.1)	12.6 (16.7)
Week 104	72	82.4 (16.2)	60.9 (27.8)	70	70.8 (24.2)	48.7 (30.3)
Change From Baseline to Week 104	72	45.4 (21.1)	46.0 (28.4)	69	35.2 (23.9)	35.8 (31.6)
LS Means (Week 104)		44.1	46.0		32.4	34.6
Difference * [MACI – Microfracture]	Difference in Pain Score: 11.8 Difference in Function Score: 11.4					
p-value **	0.001					

LS = least squares; KOOS = Knee injury and Osteoarthritis Outcome Score; SD = standard deviation; SRA = Sports and Recreational Activities.

* Difference in least squares mean values at Week 104 [MACI – Microfracture].

**p-value for difference in co-primary endpoints assessed jointly at Week 104 based on multivariate analysis of variance.

MACI® SUMMIT study

Secondary efficacy variables (ranked in order of importance in the protocol):

- Histological evaluation of structural repair of evaluable biopsies harvested from the core of the index lesion during arthroscopy at Week 104. Evaluation of histological data was performed by independent central review blinded to the patient's treatment. An appropriate histological evaluation score was used to assess the structural repair. The microscopic International Cartilage Repair Society (ICRS) II variable "Overall Assessment" was to be regarded as the most important histological assessment variable addressing the related histology efficacy endpoint
- MRI assessments of structural repair parameters at baseline and at Weeks 52 and 104 including:

  - Degree of defect fill based on the thickness of repair tissue
  - Degree of integration of the repair tissue with adjacent native cartilage
  - Signal intensity of the repair tissue relative to adjacent native cartilage
  - Change from Baseline at Weeks 52 and 104 in the above repair parameters (Note: this analysis was planned but not completed.)

  Evaluation of MRI data was performed by independent central review blinded to the patient's treatment. Appropriate MRI sequences were used to image cartilage repair tissue to allow assessment of parameters. The variable "degree of defect fill" was to be regarded as the most important MRI assessment variable addressing the related MRI efficacy endpoint

- Response rate based on KOOS Pain and Function (SRA) scores: the proportion of patients who responded to treatment at Week 104. A responder was defined as a patient with at least a 10-point improvement in both the KOOS Pain and Function (SRA) scores from Baseline
- Treatment failure rate: the proportion of patients in each treatment group assessed as treatment failures at Week 104 (Note: this analysis was planned but not completed as the low number of treatment failures made this not evaluable)

MACI® SUMMIT study - results

Secondary Efficacy endpoints (using a closed hierarchical testing procedure)

1. Histological evaluation at Week 104: comparable in the 2 groups

2. MRI assessments of structural repair parameters at Weeks 52 and 104: no statistically significant difference between the groups

3. Response rate based on KOOS Pain and Function scores at Week 104 , using a pre-defined criterion of at least a 10-point improvement from Baseline in both Pain and Function: The percentage of subjects who responded to was significantly greater for subjects in the MACI group compared to those in the microfracture group.

Table 6: KOOS Response Rate: Full Analysis Set with LOCF and MI for Missing Data

n (%)	MACI N = 72	Microfracture N = 72	p-Value
Visit 10 (Week 104) (LOCF)			
Responded	63 (87.50)	49 (68.06)	0.016
Not Responded	9 (12.50)	20 (27.78)	
Missing	0	3 (4.17)	
Visit 10 (Week 104) (MI)			
Responded	62 (86.11)	48 (66.67)	0.011
Not Responded	7 (9.72)	18 (25.00)	
Missing	3 (4.17)	6 (8.33)	

CMH = Cochran-Mantel-Haenszel; KOOS = Knee Injury and Osteoarthritis Outcome Score

p-Value: calculated for response categories 'Responded' and 'Not responded' using a CMH χ^2 Test ($\alpha = 0\ 05$) to compare between treatment groups

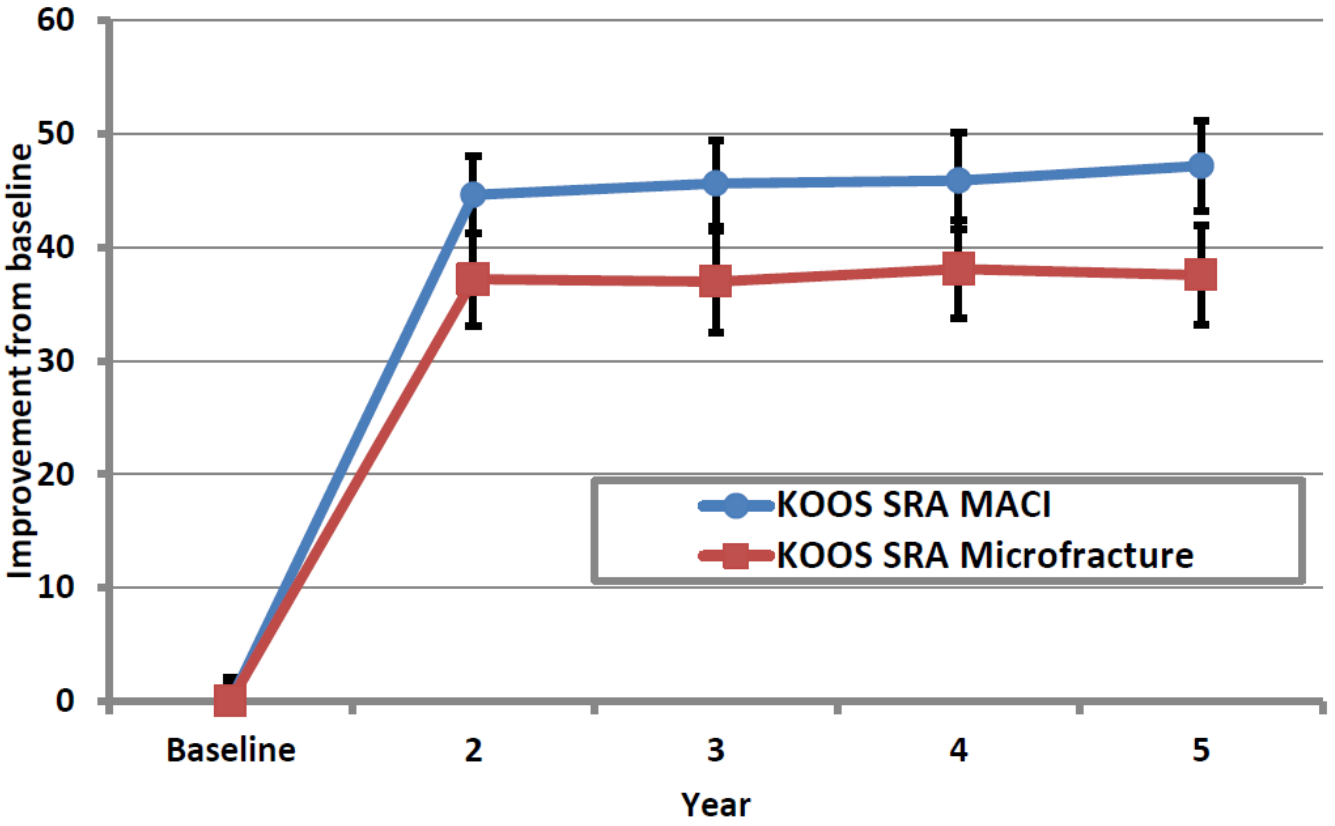
KOOS Response Rate: a patient is regarded as a responder for KOOS if a 10-point improvement in both KOOS Pain and Function (SRA) scores was achieved with respect to Baseline Otherwise, the patient is regarded as a nonresponder

US FDA MACI® assessment report

SUMMIT Extension study

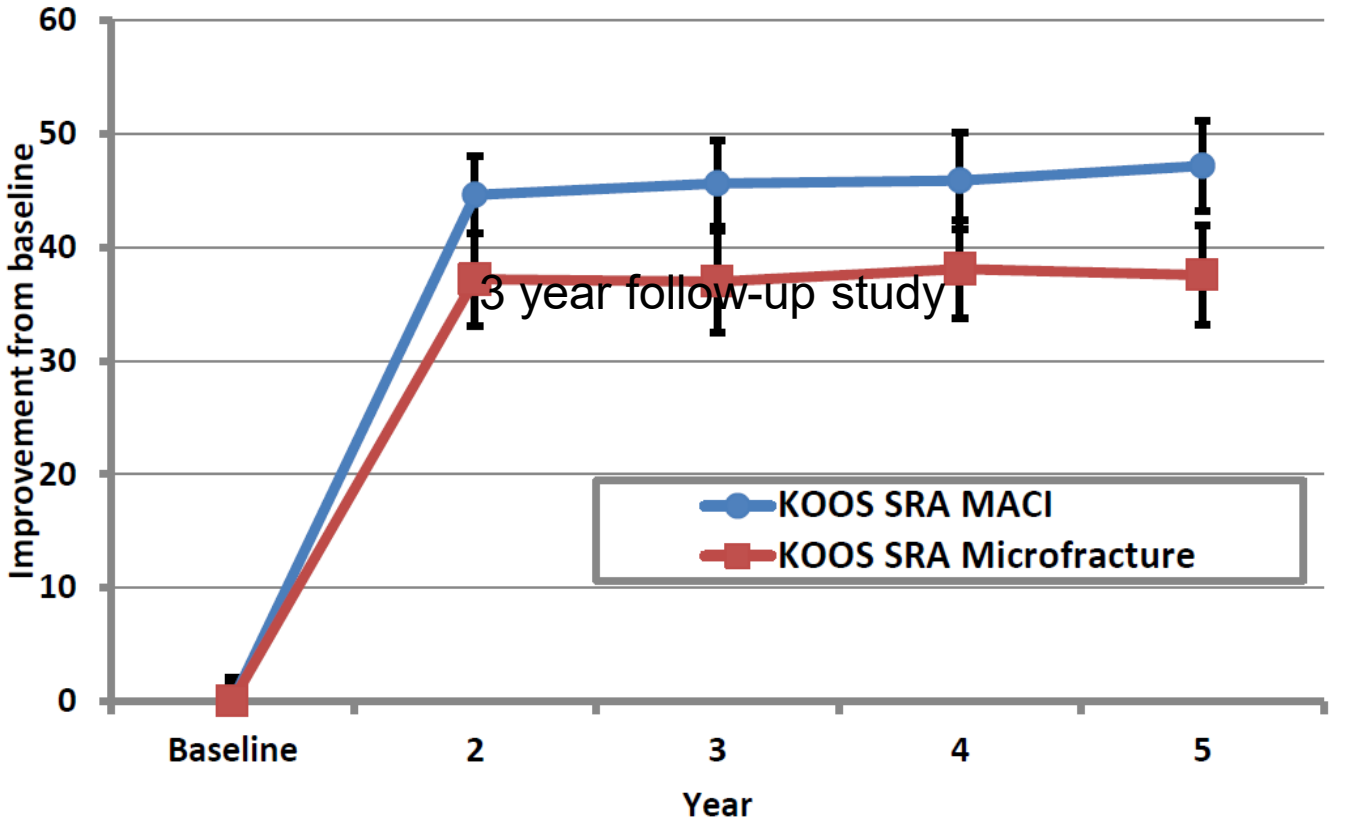
- 3 year follow-up study

Figure 2: Improvement of KOOS SRA Scores from Baseline over 5 Years +/- SE



SUMMIT Extension study

Figure 2: Improvement of KOOS SRA Scores from Baseline over 5 Years +/- SE



MACI® SUMMIT study - results

Subsequent Surgical Procedures

Table 11: Overview of Subsequent Surgical Procedures

n (%)	MAC N = 72	Microfracture N = 72
Any SSP	6 (8.3)	7 (9.7)
1 SSP	6 (8.3)	5 (6.9)
2 SSPs	0	2 (2.8)

SSP = subsequent surgical procedure

THANK YOU

財團法人醫藥品查驗中心
Center for Drug Evaluation,Taiwan