2023台灣醫事檢驗學會

從血癌的精準檢驗到CAR-T治療

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現任

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榮譽(Honor)

1. 2008年商業周刊百大良醫推薦好醫師
2. 2003、2004、2012、2018年中國醫藥大學附設醫院傑出醫師
3. 韓國、越南、亞美尼亞等多國醫師來台向巫醫師學習
4. 2008~2012年國際會議 Pan Pacific Symposium on Stem Cells and Cancer Research組織委員會委員
5. 為國際知名SCI醫學期刊論文審稿學者(reviewer)
6. 發表上百篇論文於國際知名SCI醫學期刊
7. 2019年中華民國私立教育事業會 資深暨優良教師獎
8. 指導多位碩士和博士畢業，並擔任多位碩士和博士口試委員
9. 科技部(國科會) 2014、2015、2018、2019、2021年複審會委員

Lecture Outline

1. 什麼是精準治療(precision medicine)
2. 血癌的精準檢驗和治療
3. 造血幹細胞移植(HSCT)
   半吻合造血幹細胞移植
4. 什麼是細胞/幹細胞治療
   間質幹細胞(MSC)
5. CAR-T治療
6. 台灣細胞治療的法規

什麼是精準治療(precision medicine)

Precision Medicine (精準醫療) comes from

The Right diagnosis

The Right Drug

For Right Patient (NGS)

With Right Dose (TDM)

On Right Time (MRD)

醫學檢驗是精準醫療之母!

正確診斷才能正確治療

- 主訴: 十二歲女生，因為學校健康檢查顯示貧血而至門診求診。
- 病患本身無症狀，飲食習慣正常，月經自九歲開始，目前規則28天左右來一次，每次約四～五天。
- 家族無貧血病史。
- 實驗室檢查: Hb 9.5; MCV 69; RBC 4.0x10^6 ; Platelet 455K; WBC 6500 (neutrophil: 65.3%, lymphocyte: 34.7%) 。
- Fe 13.4; TIBC 466, iron saturation: 2.8%; Ferritin 5.1
- 給予鐵劑服用後一個月，血紅素上升至11。繼續服用鐵劑至6個月。

血癌/淋巴癌的精準檢驗和治療

1. 什麼是血液疾病
2. 常見的惡性血液腫瘍: 血癌(白血病，淋巴癌...)

   # 血癌精準的的分類、診斷、治療、追蹤 (MRD)

   # Advance in leukemia

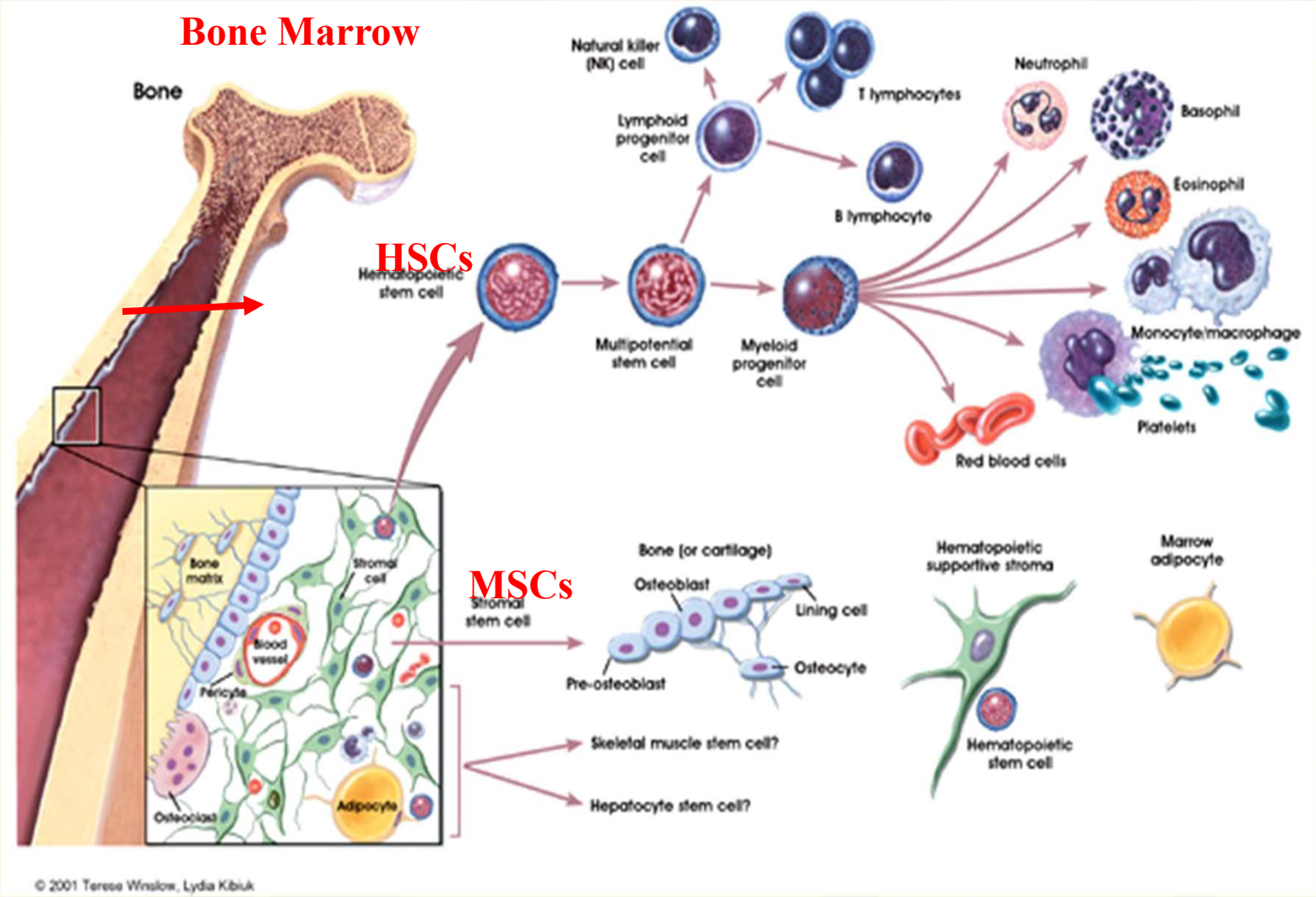
   # 傳統化療外，血液腫瘤新的治療 (新藥，標靶藥)
3. 惡性淋巴癌

- 血液疾病(Hematology)
  骨髓移植
- (恶性)腫瘤疾病(Oncology)

血液(Blood)組成

- 血液是由血球和血漿所組成。
- 血球包括紅血球、白血球和血小板，其中白血球又分為中性球、嗜酸性、嗜鹼性球、單核球、淋巴球五種。
- 所有血球都是由骨髓中的幹細胞分化而來。
- 血漿中含有各種凝血因子、酵素、白蛋白、免疫抗體及各種化學物質。

Blood


Bone Marrow
Bone
HSCs
Hematopoietic stem cell
Natural killer (NK) cell
T lymphocytes
Lymphoid progenitor cell
B lymphocyte
Neutrophil
Basophil
Eosinophil
Multipotential stem cell
Myeloid progenitor cell
Monocyte/macrophage
Platelets
Red blood cells
Bone matrix
Stromal cell
Blood vessel
Pericyte
Osteoclast
Adipocyte
MSCs
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte
© 2001 Terese Winslow, Lydia Kibiuk

什麼是血液病？

- 血液病就是指骨髓、血球(CBC)或血漿異常所造成的疾病，包括：
  - 貧血(RBC)
  - 白血球異常(WBC)
  - 出血傾向(Platelet, Coagulopathy)
  - 骨髓衰竭症候群(Bone marrow failure)
  - 血癌(白血病) (Leukemia)
  - 淋巴癌 (Lymphoma)
  - 其它血液癌症

輸血問題 (輸紅血球和血小板)

- 台灣的血液有做B肝、C肝及愛滋的篩檢，但是因為有空窗期，所以還是會有感染的危險。
- 每次輸血得B肝的機率只有6萬3千分之一；得愛滋的機率是百萬分之一；得C肝的機率為10萬3千分之一。
- 輸血感染的機會微乎其微，不必過度擔心。
- 用親人的血並不好，因為較容易產生各種副作用及排斥。

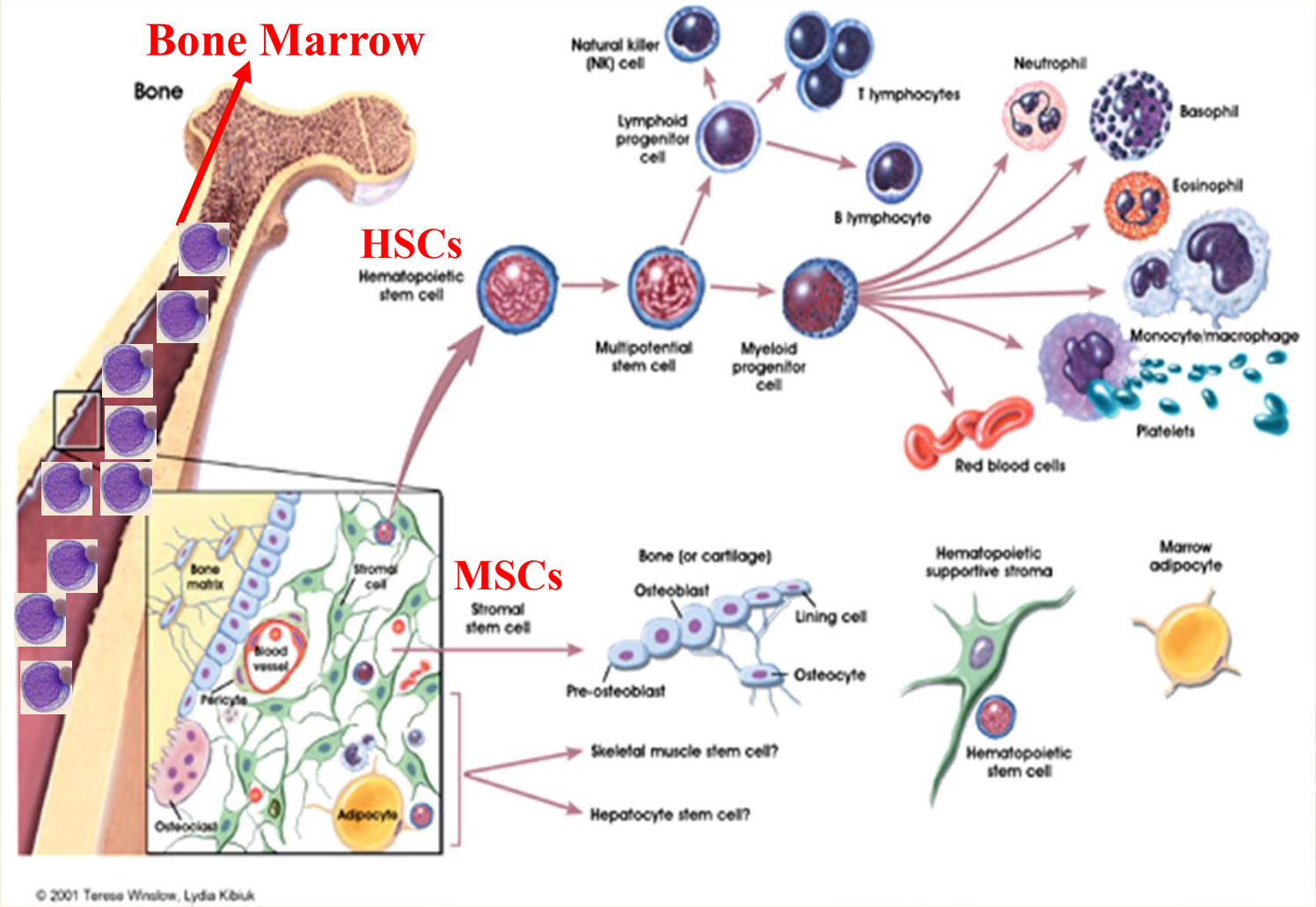
急性淋巴性白血病

- 小文是個4歲的男孩，但最近一個月來，臉色愈來 愈蒼白，輕輕碰撞，身上就出現瘀青，食慾減退， 有時也容易發燒。
- 媽媽於是帶他去看小兒科醫師，醫師注意到他已貧血及肝脾腫大的現象，就請小文去抽血，結果發現嚴重貧血，血紅素質只有5g/dl (正常4歲小孩血紅素值應大於14~45萬/mm^3)，白血球數目4萬3千/mm^3 血球(白血球正常值4千~1萬/mm3)，而且不正常的血癌細胞佔了白血球總數的94%。
- 檢查結果小文罹患了急性淋巴性白血病，必須接受2年半的化學治療。

The leukemias

- are the most common malignancy in childhood (about 30%-40% of childhood cancers)
- defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to a clonal proliferation of cells.
- the progeny of these cells have a growth advantage over normal cellular elements owing to an increase rate of proliferation, a decreased rate of spontaneous apoptosis, or both
- this result is a disruption of normal marrow function and, ultimately, marrow failure

The location of leukemia is Bone marrow



一般白血病的型態分類

急性白血病	急性淋巴性白血球
	急性骨髓性白血病
慢性白血病	慢性淋巴性白血球
	慢性骨髓性白血病： 成人型(BCR-ABL)、幼年型

兒童白血病的治癒率比成人高很多，特別是兒童急性淋巴性白血球約有80-90%的治癒率!!!

幼年型慢性骨髓性白血病需要做骨髓移植

印尼童罹慢性骨髓性白血病 媽媽的雇主助她在台接受骨髓移植

2020/06/02 21:17

血癌臨床症狀

發病時間非常短，約幾個星期。其症狀如下：

1. 貧血
2. 出血：正常血小板因血癌細胞侵犯無法形成，容易出現瘀青、出血斑點...等。
3. 骨頭疼痛
4. 不明原因發熱
5. 器官腫大：血癌細胞侵犯到肝臟、脾臟、淋巴腺、胸腺等，造成器官腫大

Diagnosis of leukemia

- Symptoms and signs
- PE: lymphadenopathy, hepatosplenomegaly…
- Lab:
  - CBC: anemia, thrombocytopennia, leukopenia or leukocytosis (有時CBC會完全正常)
  - Peripheral blood smear: leukemic cells (mimicking as atypical lymphocytes or lymphocytes)
  - Bone marrow aspiration/biopsy: morphology, immunophenotyping, karyotype/molecular analysis

DDx of leukemia

- Primary bone marrow failure: aplastic anemia
- Failure of a single cell line: ITP, congenital neutropenia,
- Infection: infectious mononucleosis, hemophagocytic syndrome
- Other malignancy that may invade the bone marrow: neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, retinoblastoma

Diagnosis in leukemia

1. Morphology/Cytochemistry (FAB Classification)
2. Immunophenotyping (cell marker)
3. Cytogenetics/karyotype (chromosome study)
4. Molecular biology

   Fuorescent *in situ* hybridization (FISH)

   Polymerase chain reaction (PCR): oncogene

   DNA microarray

Morphology/Cytochemistry (FAB Classification)

FAB designation	% of total	Prominent features
ALL		
L1	82	Small blasts with scanty cytoplasm, regular nuclear shape, fine-to-slightly coarse chromatin and inconspicuous nucleoli, often with an admixture of larger blasts
L2	15	Large and heterogeneous blasts with abundant cytoplasm, irregularly shaped nuclei, variable chromatin pattern, and prominent nucleoli, often with an admixture of smaller blasts
L3	3	Large and homogeneous blasts with finely stippled chromatin, prominent nucleoli, and abundant deep-blue cytoplasm, often with vacuolation
AML		
M0	2	Large and agranular blasts with minimal myeloid differentiation; negative myeloperoxidase and Sudan black B by cytochemistry; expression of at least one myeloid antigen (e.g., CD13, CD33)
M1	10–18	Poorly differentiated myeloblasts with occasional Auer rods
M2	27–29	Myeloblasts with granulocytic differentiation;<20% monoblasts; Auer rods may be prominent
M3	5–10	Hypergranular, abnormal promyelocytes with bundles of Auer rods (faggot cells) and often reniform or grooved bilobed nuclei (M3h); M3v variant characterized by bilobed or grooved nuclei, a few fine granules, and infrequent Auer rods
M4	16–25	Myeloblastic and monoblastic differentiation (20–80% of nonerythroid cells are monoblastic and 20–80% are myeloblastic); M4Eo variant associated with >5% dysplastic eosinophilic precursors in marrow
M5	13–22	Monoblastic differentiation; M5a subtype has predominance of monoblasts (≥80% of leukemic cells); M5b subtype shows differentiation of some monocytic precursors
M6	1–3	Myeloblastic leukemia with dyserythropoiesis and megaloblastoid features (M6a), or leukemia with erythroblastic differentiation (M6b)
M7	4–8	Megakaryoblastic differentiation, with frequent bone marrow fibrosis

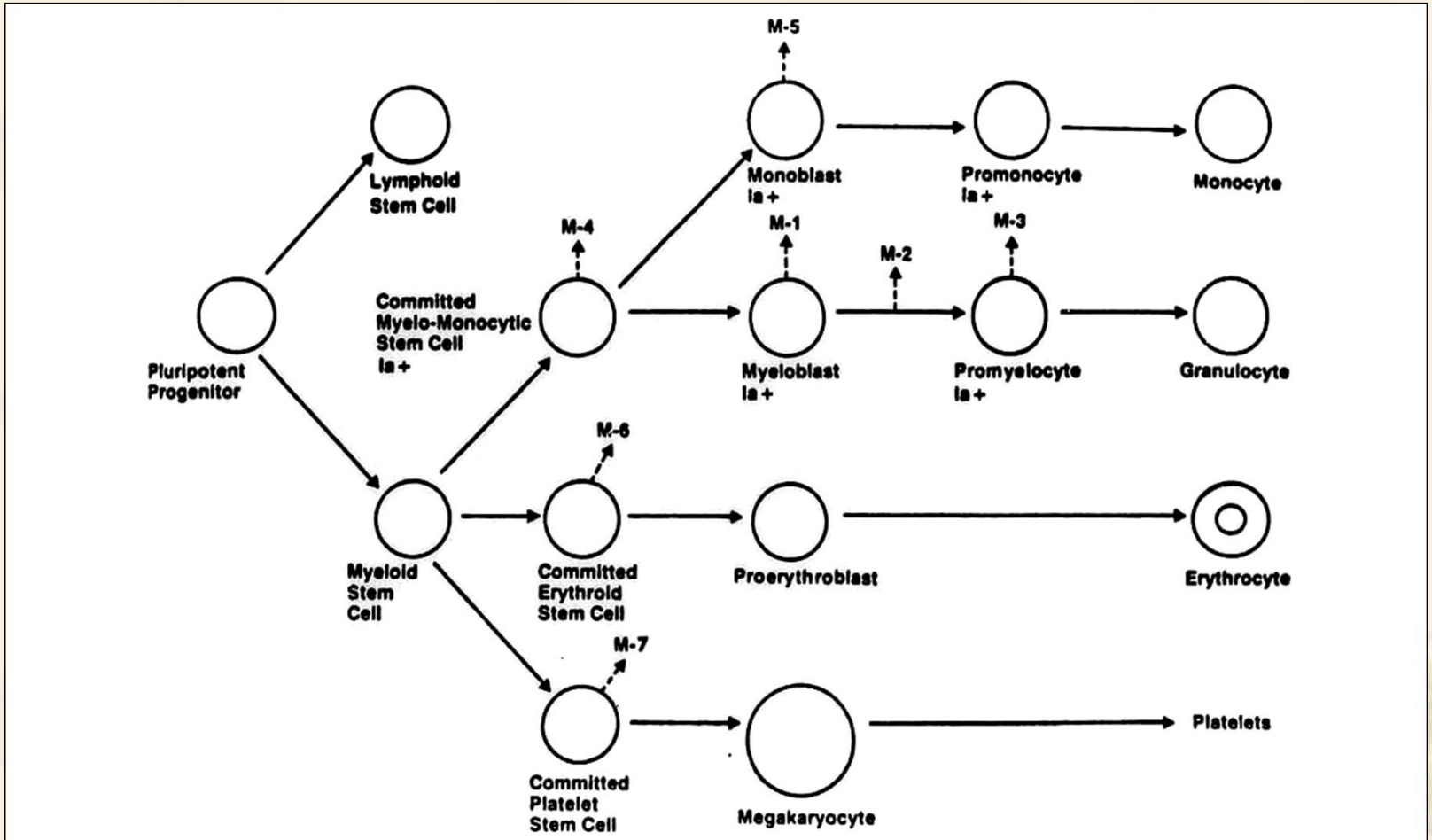


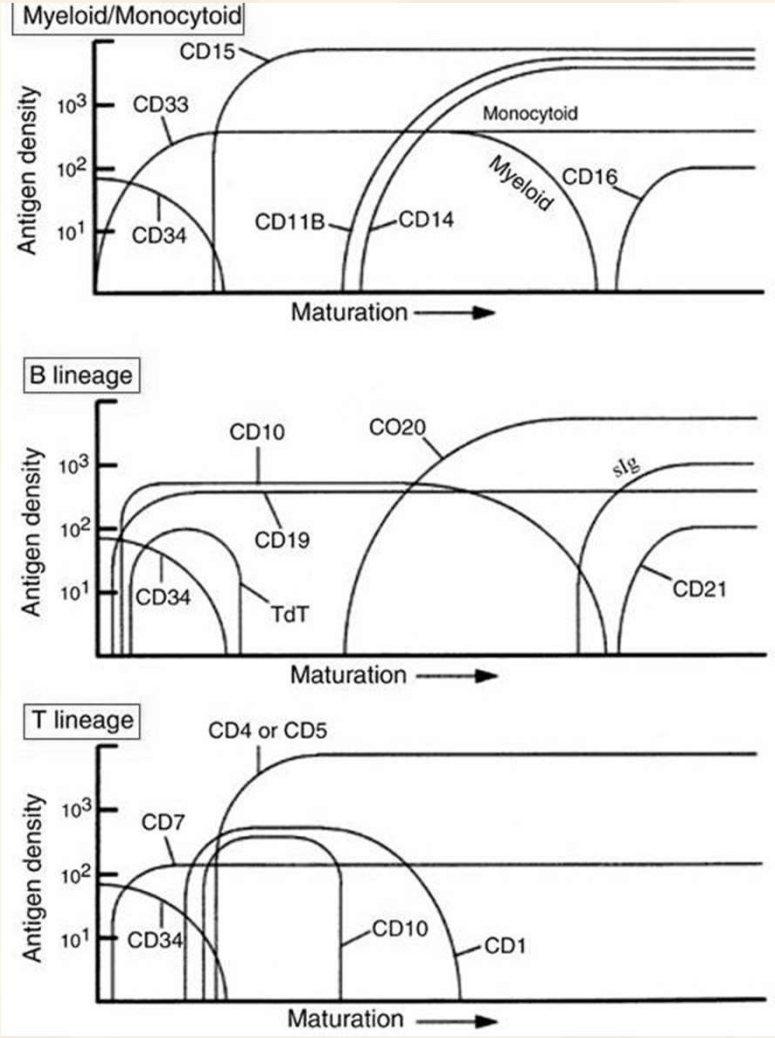
Fig. 20-1. Myeloid differentiation and relationship to FAB classification of ANLLs. M1, undifferentiated myeloid; M2, early (?) differentiated myeloid; M3, promyelocytic; M4, myelomonocytic; M5, monocytic; M6, erythroleukemia; M7, megakaryocytic. (Modified from Foon KA, Schroff RW, and Gale RP: Blood 60:1, 1982.)

Cytochemical stains in acute leukemia

- PAS: ALL
- POX: MPO (myeloperoxidase): Myeloid granules (M1,M2,M3,M4)
- ANBE (Alpha-naphthyl butyrate esterase)→Monocytoid (M4,M5)

Immunophenotyping (cell marker)

血球細胞的”身份證”


Myeloid/Monocytoid
Antigen density
10^3
10^2
10^1
CD15
CD33
Monocytoid
Myeloid
CD16
CD34
CD11B
CD14
Maturation
B lineage
Antigen density
10^3
10^2
10^1
CD10
CO20
sIg
CD19
CD34
TdT
CD21
Maturation
T lineage
Antigen density
10^3
10^2
10^1
CD4 or CD5
CD7
CD34
CD10
CD1
Maturation

Immunologic classification of ALL

Table 7.3. *Immunologic classification of ALL*

Immunologic subtype	Immunologic marker study (% of cases positive for marker)										Frequency of subtype
	CD19	CD22	CD79[a]	CD10	CD7	CD5	CD3[a]	clgμ	slgμ	slgκ or λ	
Early pre-B	100	98	99	95	5	0	0	0	0	0	60–65%
Pre-B	100	100	100	98	0	<2	0	100	0	0	20–25%
Transitional pre-B	100	100	100	50	0	0	0	100	100	0	1–3%
B	100	100	100	50	0	0	0	98[b]	98[b]	98[b]	2–3%
T	<5	0	0	45	100	95	100	0	0	0	15–18%

Abbreviations: cIg, cytoplasmic immunoglobulin, sIg, surface immunoglobulin.

[a] Cytoplasmic expression.

[b] Approximately 2% of FAB-L3, B-lineage ALLs with a t(8;14), t(2;8), or t(8;22) translocation may express no cIg or neither cIg nor sIg.

Immunologic Classification of AML

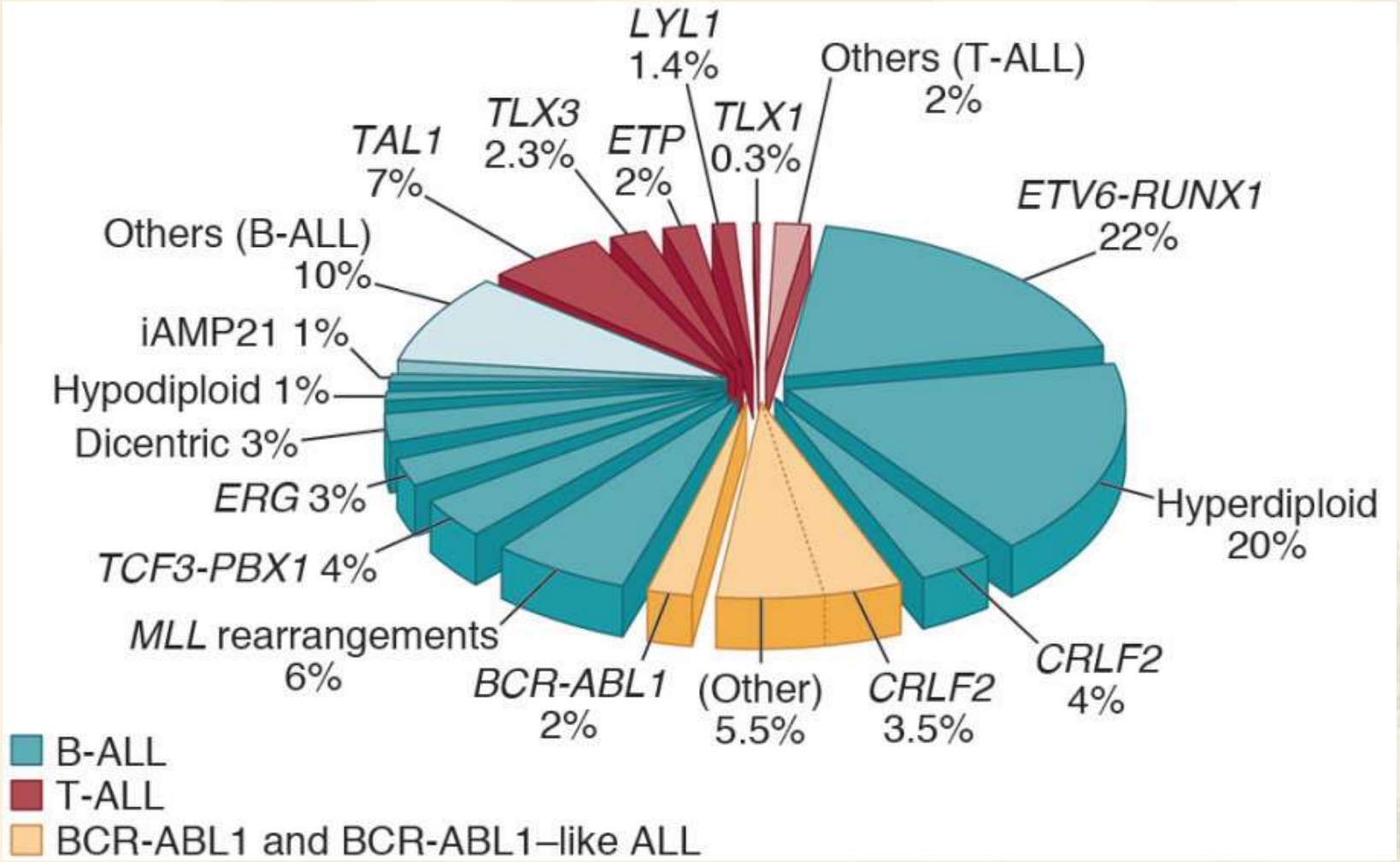
Table 7.5. *Antigenic profiles of acute myeloid leukemia subgroups*[a]

FAB subtype	CD34	DR	CD13	CD14	CD15	CD33	CD41a	GPA
M0	++	++	++	0	+	++	0	0
M1	++	++	++	0	++	++	0	0
M2	++	+++	+++	0	++	+++	0	0
M3	±	±	+++	0	++	+++	0	0
M4	++	+++	++	++	++	+++	0[b]	0
M5	±	+++	++	++	++	+++	0[b]	0
M6	+	++	++	0	+	++	0	+++
M7	+	+	+	0	+	++	+++	±

Common Chromosomal Abnormalities in the Acute Leukemias of Childhood

Disease, Subtype	Chromosomal Abnormality	Influence on Prognosis
ALL, pre-B	t(12;21)	Favorable
ALL, pre-B (infantile)	t4;11)	Unfavorable
ALL, pre-B	t(9;22)	Unfavorable
ALL, B-cell	t(8;14)	None
ALL (general)	hyperdiploidy	Favorable
ALL (general)	hypodiploidy	Unfavorable
AML, M2	t(8;21)	Favorable
AML, M3	t(15;17)	Favorable
AML, M4	inv(16)	Favorable

Frequency of cytogenetic subtypes of pediatric ALL



Risk factors in childhood ALL

Pre-treatment:

- Age: infantile ALL (<1y/o, poor prognosis)
- Initial WBC: 剛開始發病的 WBC count越高表示leukemia的behavior會aggressive（就是越惡性)
- Organ involved (CNS, Testis, but not thymus, liver/spleen)
- Cell marker
- Cytogenetic/ Oncogene

After-treatment

- Speed of treatment response
- Minimal residual disease/leukemia (MRD)

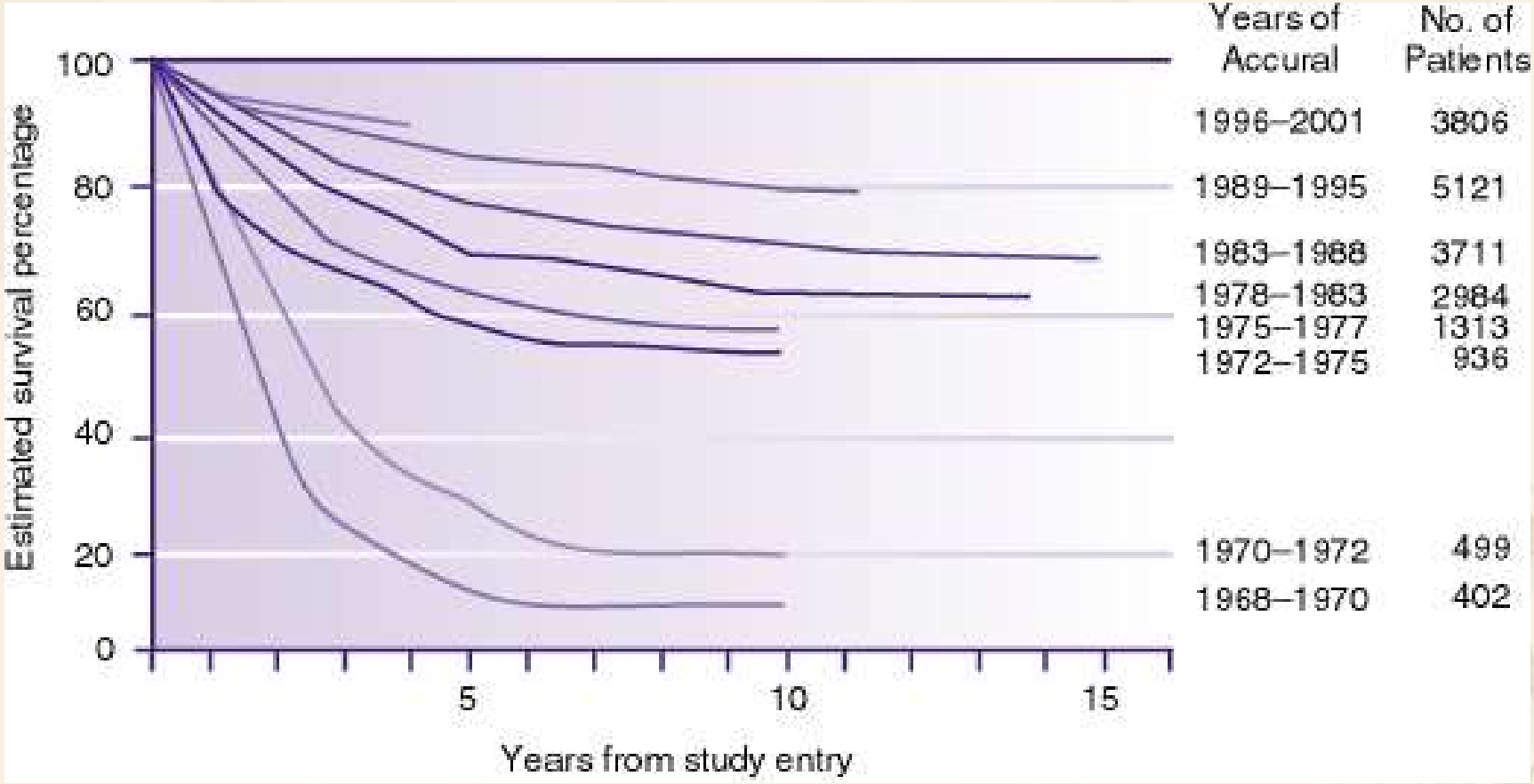
ALL的治療: 根據risk 決定用那種治療

- Chemotherapy (according Taiwan Pediatric Oncology Group (TPOG) ALL protocol):
  - ALL-2002: SR, HR and VHR
  - TPOG Infant
  - ALLTPOG 98 B-NHL (R3)：L3 ALL
- Stem Cell Transplantation (bone marrow transplantation)
- Adding target therapy?

Indication for “very high risk” chemotherapy protocol

1. WBC > 100,000 /μl, (2) T-cell
2. Hypodiploidy (chromosome ≤ 44)
3. t(9;22)/BCR-ABL fusion (improved after adding TKI inhibitor drugs)
4. t(4;11)/MLL-AF4 fusion/other MLL gene rearrangements
5. Other poor prognosis genes!!
6. Poor MRD decrease after treatment

Survival rates of children with ALL



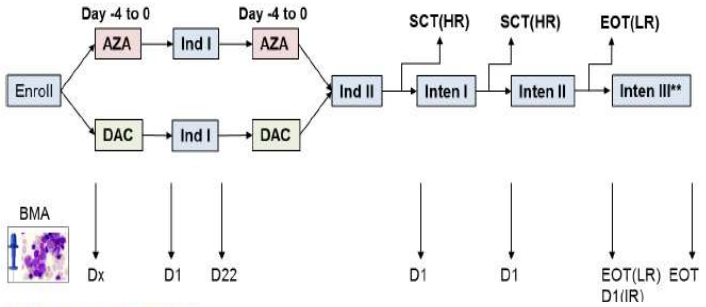
Treatment in childhood AML

- Controversial issue (chemotherapy vs SCT)
- Chemotherapy:

  usually be suggested in chromosome indicative good prognosis: t(8;21), t(15;17), inv(16)(p13q22)

- Stem Cell Transplantation (SCT):
  1. suggested in chromosome/genes indicative poor prognosis
  2. poor MRD decrease after treatment

Protocol of treatment for AML



RISK STRATIFICATION

Low-risk (LR) criteria (4 courses of chemo, not eligible for SCT)

- inv16, t(8;21), NPM1, or CEBPA AND MRD less than 0.1% after induction I

Intermediate-risk (IR) criteria (5 courses of chemo, not eligible for SCT)

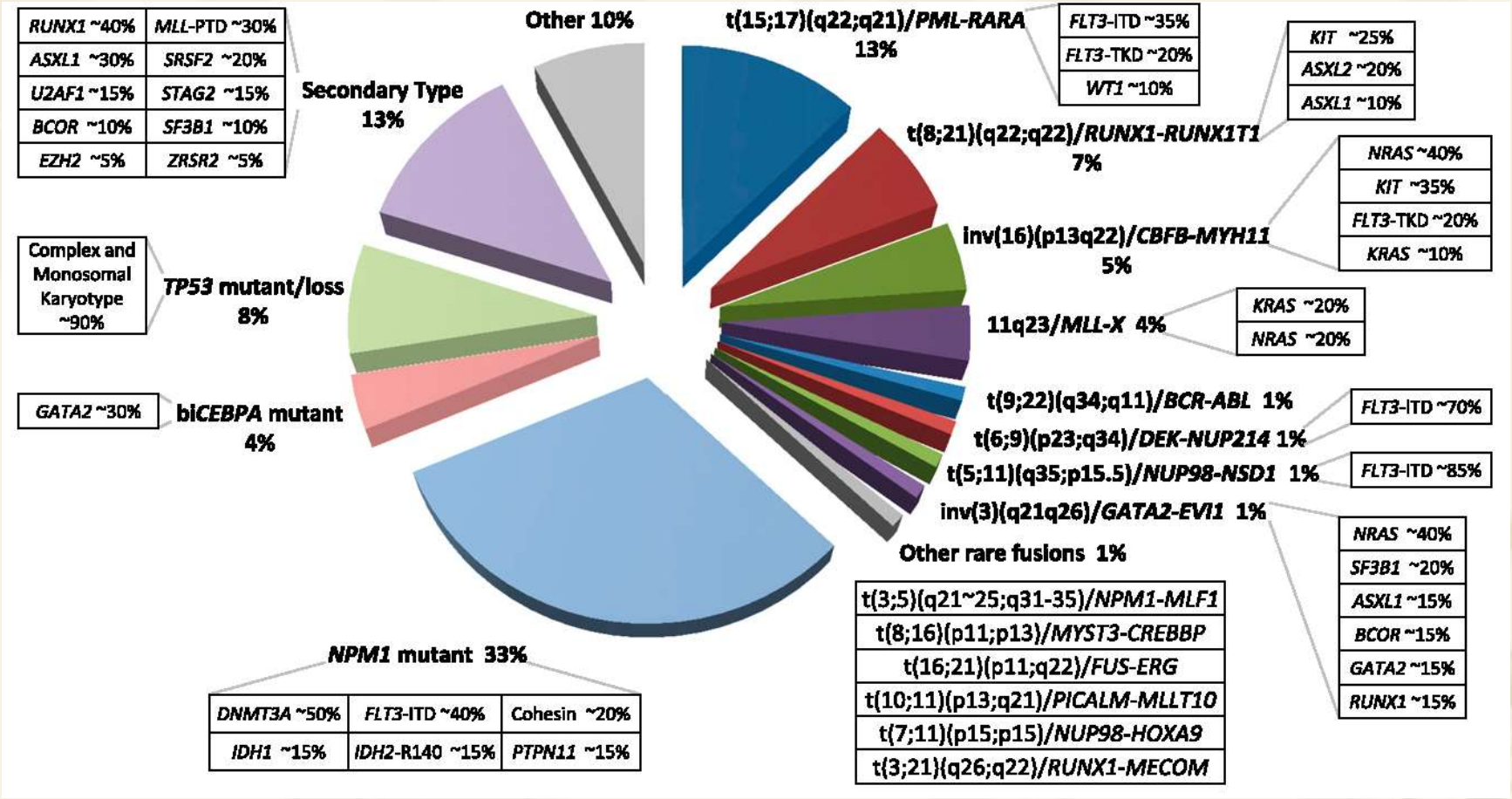
- Absence of low or high risk features

High-risk (HR) criteria (candidates for SCT)

Presence of any of the following:

- DEK-NUP214 [t(6;9)], KAT6A-CREBBP [t(8;16)], -7, -5, 5q-, KMT2A-MLLT10 [t(6;11)], KMT2A-MLLT4 [t(10;11)], inv(3)(q21q26.2), CBFA2T3-GLIS2 [inv(16)(p13.3q24.3)], NUP98-KDM5A [t(11;12)(p15;p13)], ETV6-HLXB [t(7;12)(q36;p13)], NUP98-HOXA9 [t(7;11)(p15.4;p15)], NUP98-NSD1
- Patients carrying FLT3-ITD in combination with either NUP98-NSD1 fusion or WT1 mutation
- AML with minimal differentiation or Acute Erythroid Leukemia
- Acute Megakaryoblastic Leukemia with KMT2A rearrangements, CBFA2T3-GLIS2 [inv(16)(p13.3q24.3)], or NUP98-KDM5A [t(11;12)(p15;p13)]. All other Acute Megakaryoblastic Leukemia subtypes will be considered intermediate risk.
- Treatment-related (secondary) AML
- Refractory anemia with excessive blasts and >10% bone marrow blasts (RAEB-2) or AML arising from prior MDS
- All other patients with poor response to therapy (must have one of the following features)
  - MRD ≥ 1% after Induction I
  - MRD ≥ 0.1% after Induction II

Distribution of cytogenetically and molecularly defined subsets of AML presenting in younger adults



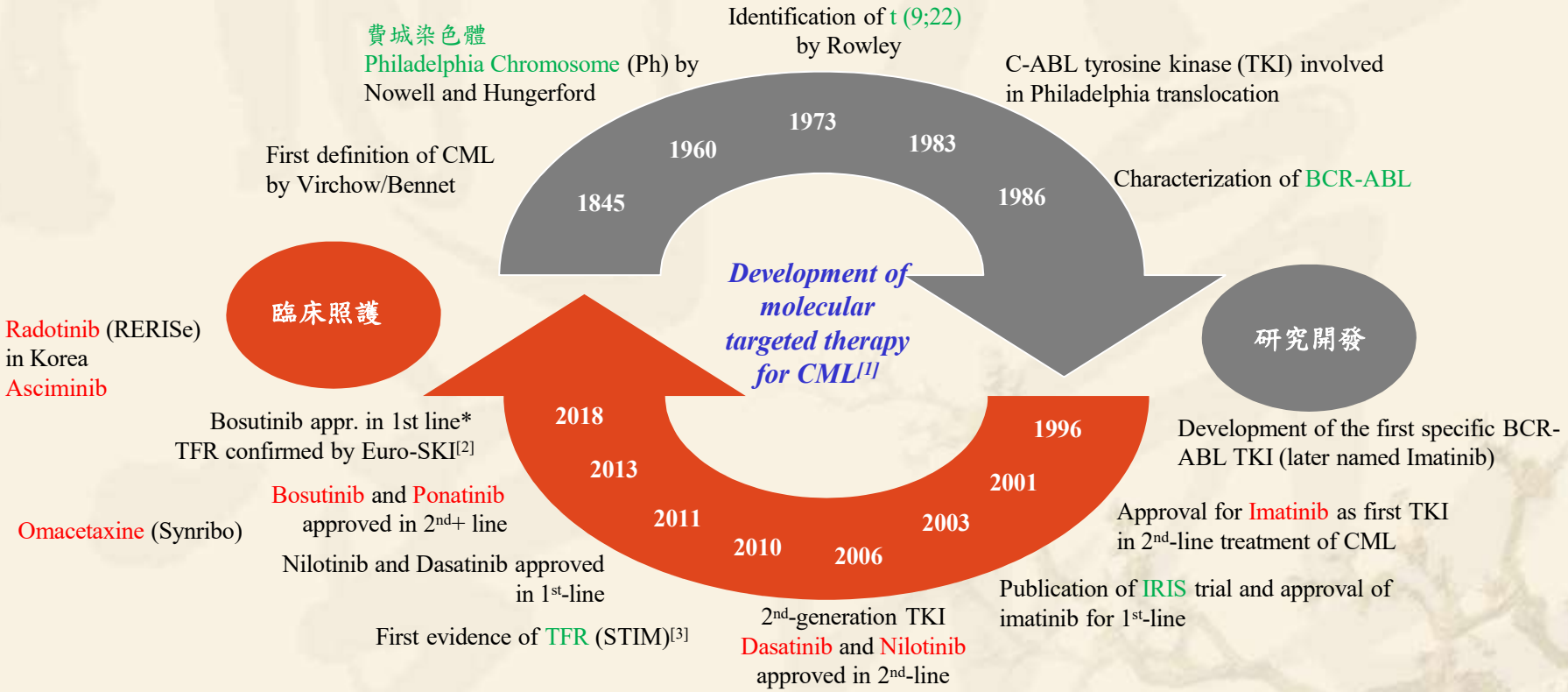
Advance in leukemia

- Molecular diagnosis (NGS, RNAseq)
- Minimal residual disease (MRD) follow up
- Target therapy drugs
- New drugs beyond tranditional chemotherapy
  Traditional (eg: Azacitidine and venetoclax…)
- Haploidentical hematopoietic stem cell transplantation
- CAR-T therapy

血液腫瘤治療方式選擇

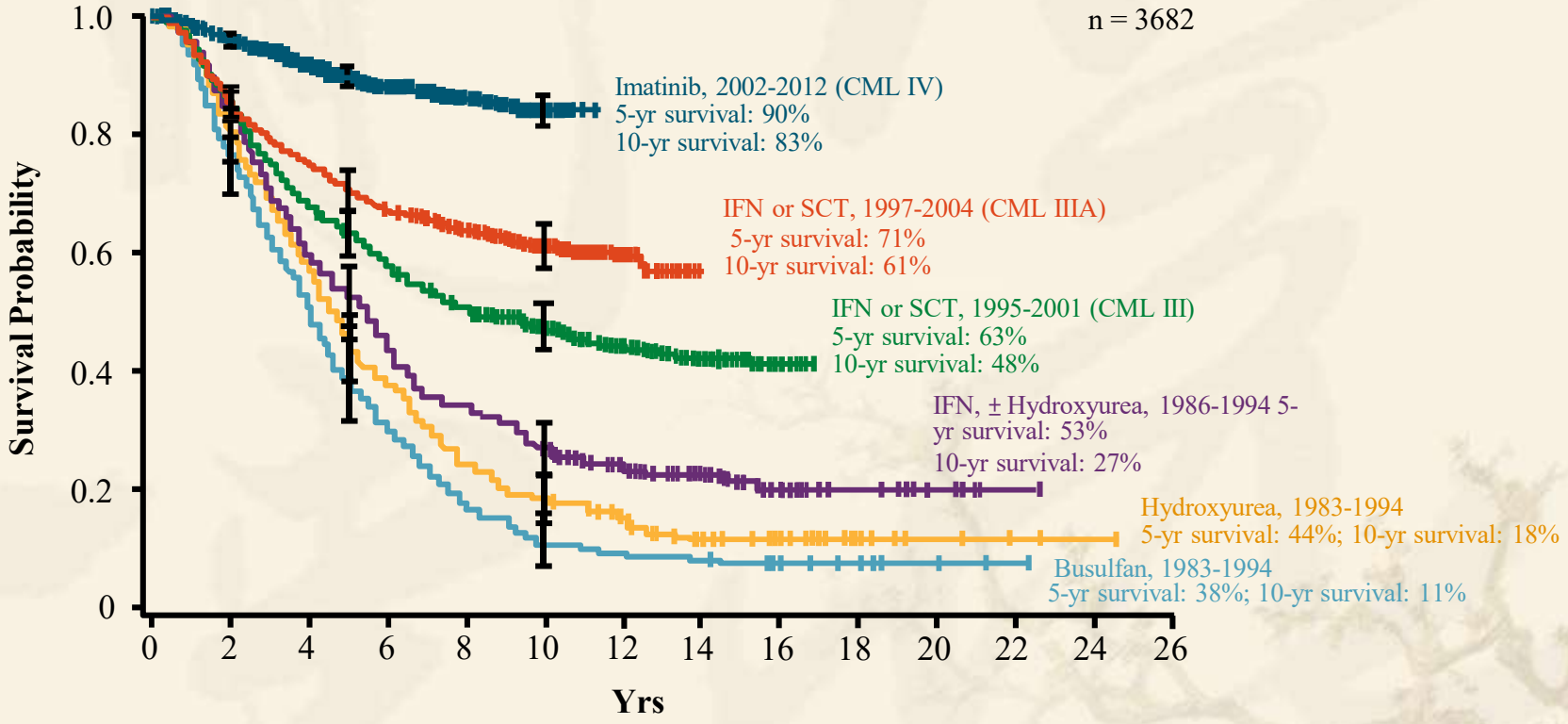
- 化學治療
- 單株抗體療法(多數合併化學治療)
- 小分子標靶/小分子激酶抑制劑(多數合併化學治療)
- 免疫治療: 雙特異抗體治療 (BiTe)、Checkpoint 抑制劑、嵌合抗原受體 T细胞 (CART) 治療
- 骨髓移植或周邊血液幹細胞移植: 自體或異體
- 局部治療: 放射線治療(俗稱電療)/開刀治療/照光治療

慢性骨髓性白血病(CML):
血液腫瘤疾病標靶藥物最成功的典範



1. Balabanov. Drug Discov Today Technol. 2014;11:89. 2. Saussele. Lancet Oncol. 2018;19:747. 3. Mahon. Lancet Oncol. 2010;11:1029.

慢性骨髓性白血病存活率:
德國研究團隊的長期經驗



Hehlmann. Haematologica 2016;101:657.
CML Database, NTUH, Tang JL, Hsu SC, et al

TKIs for adult-type CML

Personalized Medicine:

急性血癌個人化醫療的現在與未來

Enabling replicative immortality

- CD70 MoAb; CD47 MoAb

Genome instability and mutations

- 7+3, FLAG-IDA, HMAs, cytarabine, LDAC, cladribine, Vyxeos, ASTX727, fludarabine, busulfan, mitoxantrone
- GO, SGN-33a
- SCT allowing for chemotoxic conditioning regimens

Tumor micro-environment

- **Checkpoint ⊥ (PD1/PDL-1):** nivolumab, pembrolizumab, atezolizumab, durvalumab
- CAR-T, BiTE
- SCT (graft vs leukaemia), DLI

Resisting cell death

- **Pro-survival protein ⊥:** venetoclax (BCL-2), navitoclax (BCL-2+BCL-XL), AMG-176 (MCL-1)
- **TRAIL agonist:** ABBV-621
- **NEDD8/proteasome:** pevonedistat

Avoiding immune destruction

Deregulating cellular energetics

- **IDH1/2 ⊥:** enasidenib, ivosidenib

Epigenetic plasticity

- **BET ⊥:** ABBV-075 (mivebresib)
- **HDAC ⊥:** pracinostat

Evading Growth Suppression

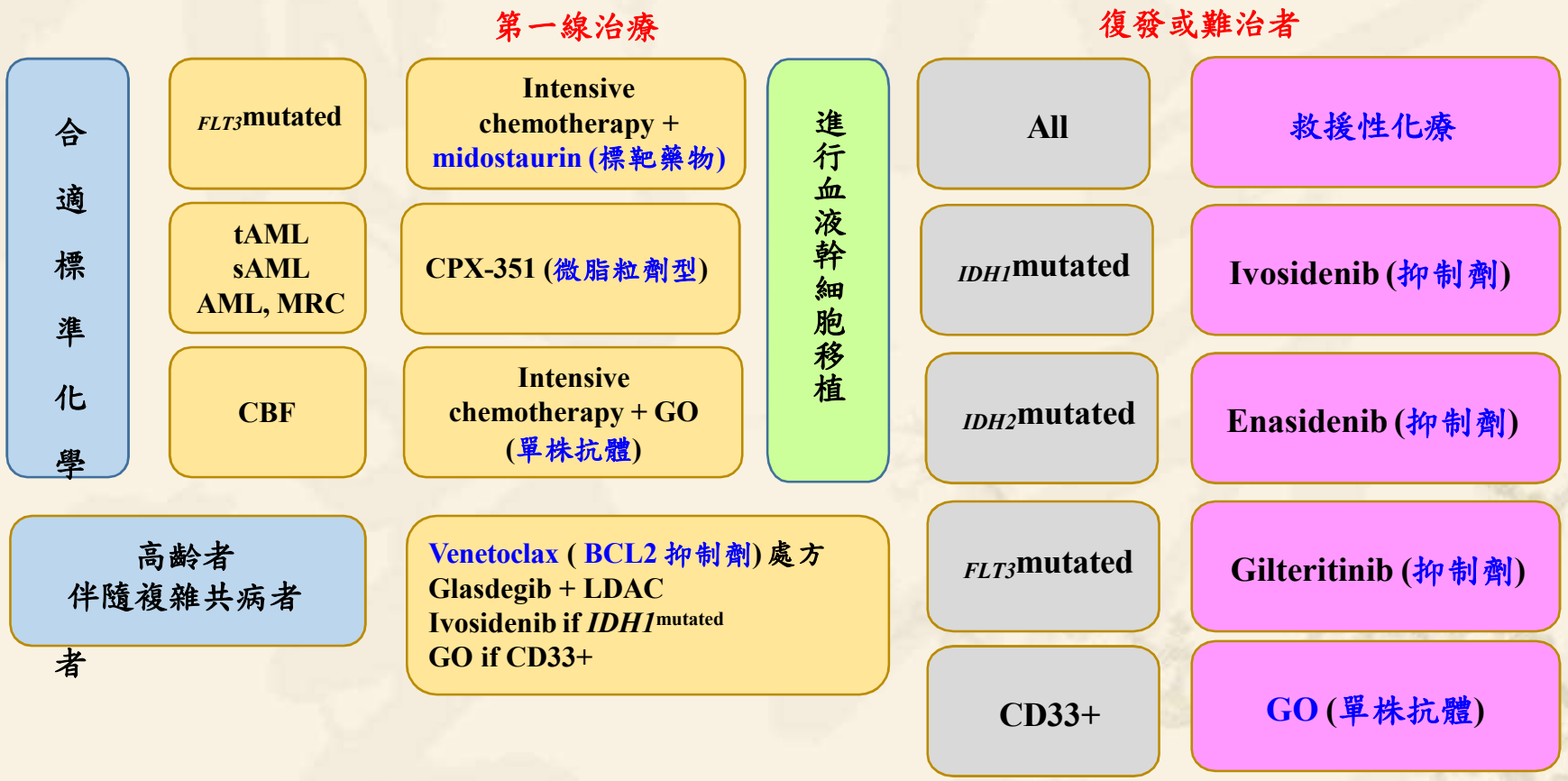
- **FLT3 ⊥**: midostaurin, quizartinib, gilteritinib, crenolanib
- **RAS ⊥**: trametinib
- **MEK ⊥**: cobimetinib
- **Tyrosine kinase ⊥**: sorafenib
- **SHH ⊥**: glasdegib
- **CDK-1 & CDK9 ⊥**: dinaciclib & alvocidib
- **JAK ⊥**: ruxolitinib
- **SINE**: selinexor†
- **TP53:** APR246

Sustaining proliferative signals

⊥ inhibitor

Modified from the slides from Dr Hagop Kantarjian in 2019 ECHO Meeting

急性骨髓性白血病(AML)
精準治療的世代



淋巴癌與淋巴性白血病標靶藥物

1. 單株抗體療法(多數合併化學治療)
   - B 細胞型淋巴癌 (CD 20) ->莫須瘤、癌即瓦輸注反應與免疫抑制
   - 何杰金氏淋巴癌/CD30(+)淋巴瘤->雅詩力 (Brentuximab vedotin) 神經毒性與骨髓抑制毒性
2. 小分子標靶/小分子激酶抑制劑(多數合併化學治療)
   - BTK 抑制劑->Ibrutinib
   - Proteasome 抑制劑-> Bortezomib
   - BCL2 抑制劑->Venetoclax
3. 免疫治療: 雙特異抗體治療(BiTe)、Checkpoint 抑制劑
4. 嵌合抗原受體T细胞 (CART) 治療

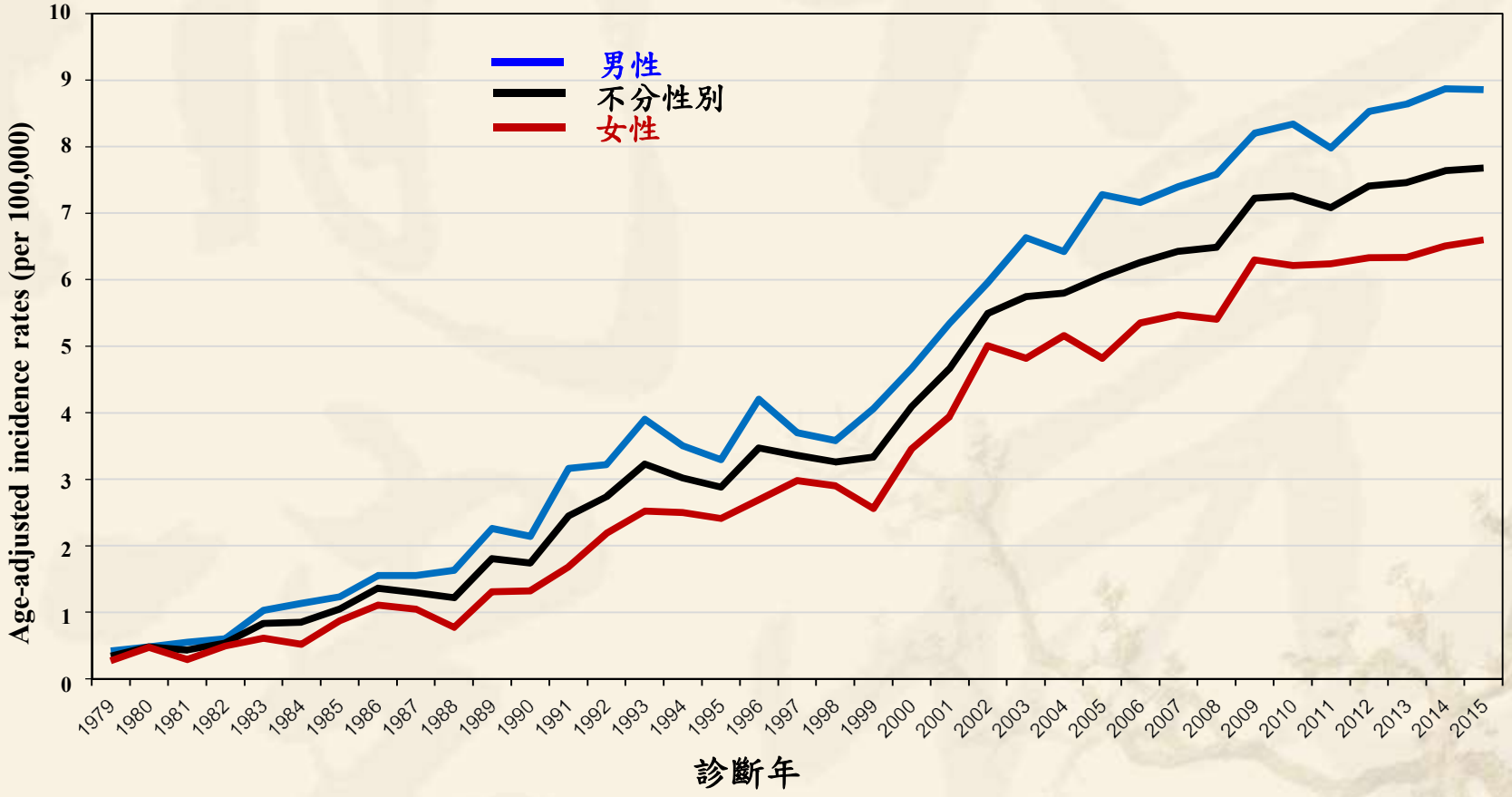
惡性淋巴瘤案例

章章是個13歲的男孩，正值活潑好動的年齡。但是這2個星期來，他卻不斷的咳嗽，吃藥也不見改善，接著**右頸部的淋巴腺也腫大**，直徑約有4公分，壓下去並不會疼痛，頷下也出現了淋巴腺腫大，漸漸地他覺得呼吸困難，爸爸趕快帶他去大醫院急診看醫師。

急診的小兒科醫師發現章章左側肺的呼吸因幾乎無法聽見，於是幫章章照了1 張胸部X光，X光顯示胸部縱隔腔腫瘤並合併左側肋膜積水，把正常左肺擠壓得剩下一小塊，所以造成咳嗽及呼吸困難。

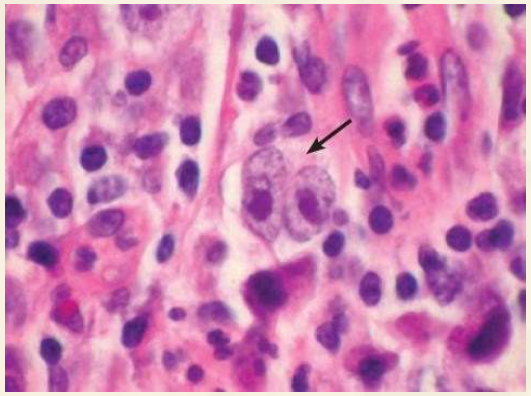
章章住進小兒科病房，醫師幫章章放置胸管，引流出肋膜積水，肋膜積水也送去化驗，可看到淋巴瘤細胞，醫師也為章章頸部的淋巴腫塊做了切片檢查，病理報告指出章章患有**惡性淋巴瘤**。

台灣非何杰金氏淋巴瘤(NHL)的發生率



衛福部國建署台灣癌症資料庫

2016 世界衛生組織
約 100 種淋巴瘤亞型



RS 細胞

- 淋巴瘤
  - 何杰金氏
  - 非何杰金氏
    - **B-細胞**
      - 瀰漫性大細胞型
      - 濾泡細胞型
      - 被套細胞型
      - 邊緣細胞型
      - 淋巴漿細胞型
      - 小細胞型
      - 淋巴芽性型
      - ……
    - **T/NK-細胞** 周邊細胞型 淋巴芽型
      - 鼻腔中線型
      - 皮膚型
      - 分化不良型 血管芽型
      - 腸道型
      - ……
    - 其他

Non-Hodgkin's Lymphoma (NHL)

- Cell origin:

  T-, or B-, or indeterminate cells

- Involved tissue:

  lymphonode, extranode

- Childhood NHL represent a heterogeneous group of disorders that are quite different from adult NHL:
  - almost invariably disseminated
  - diffuse not nodular
  - high-grade malignancies of immature T- or B-cell lineage
  - with frequent extra-nodal disease, bone marrow and/or CNS involvement

Lymph node sites

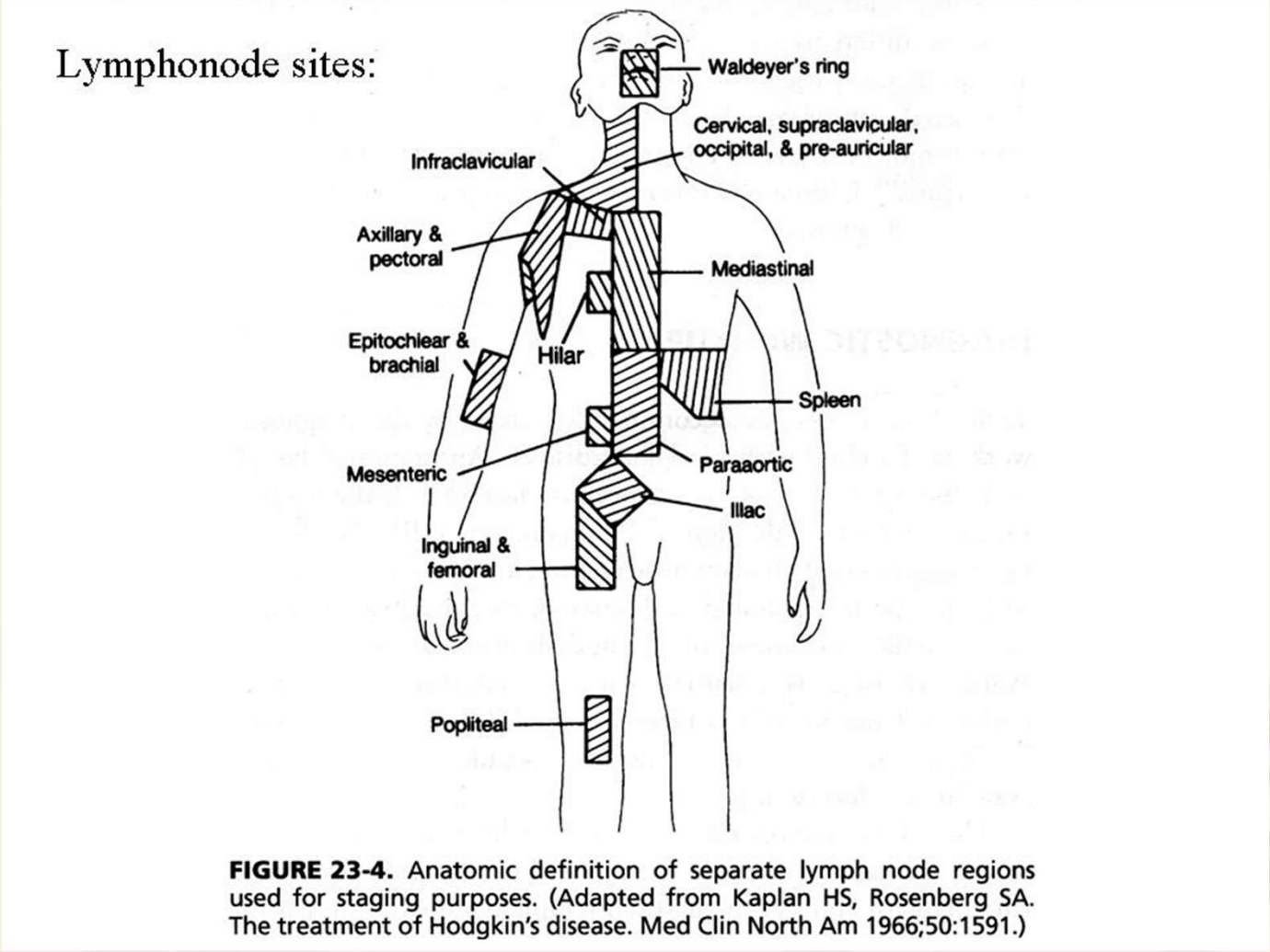
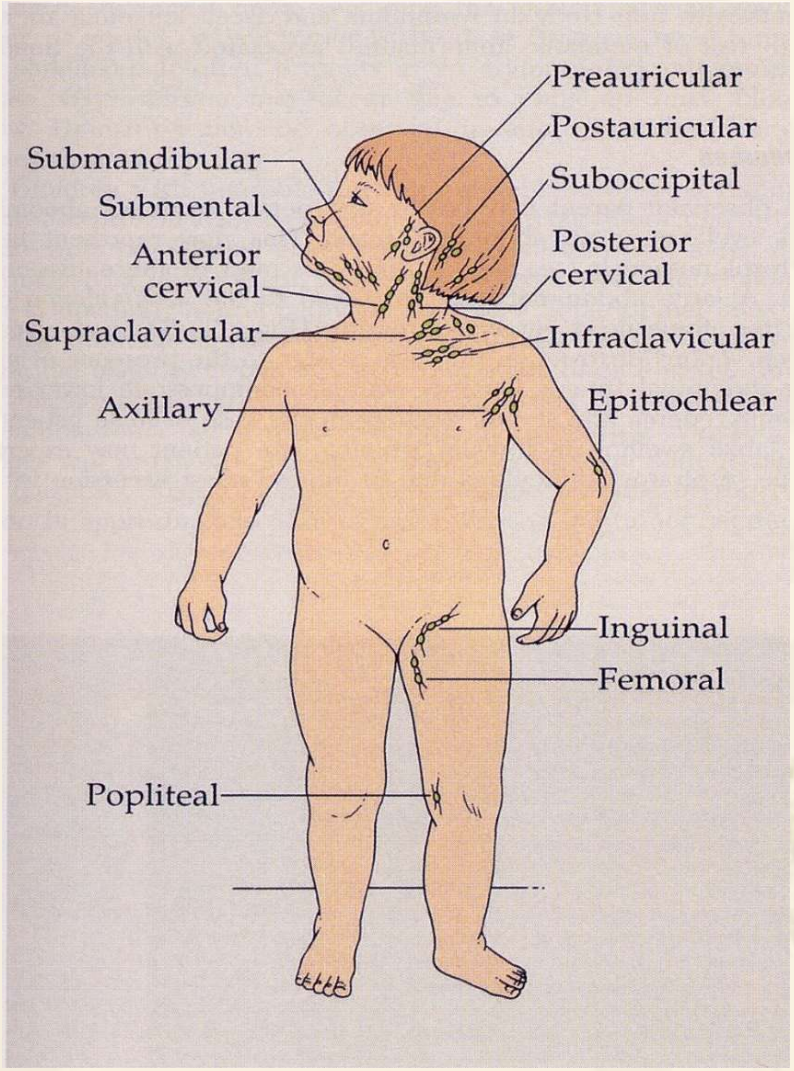
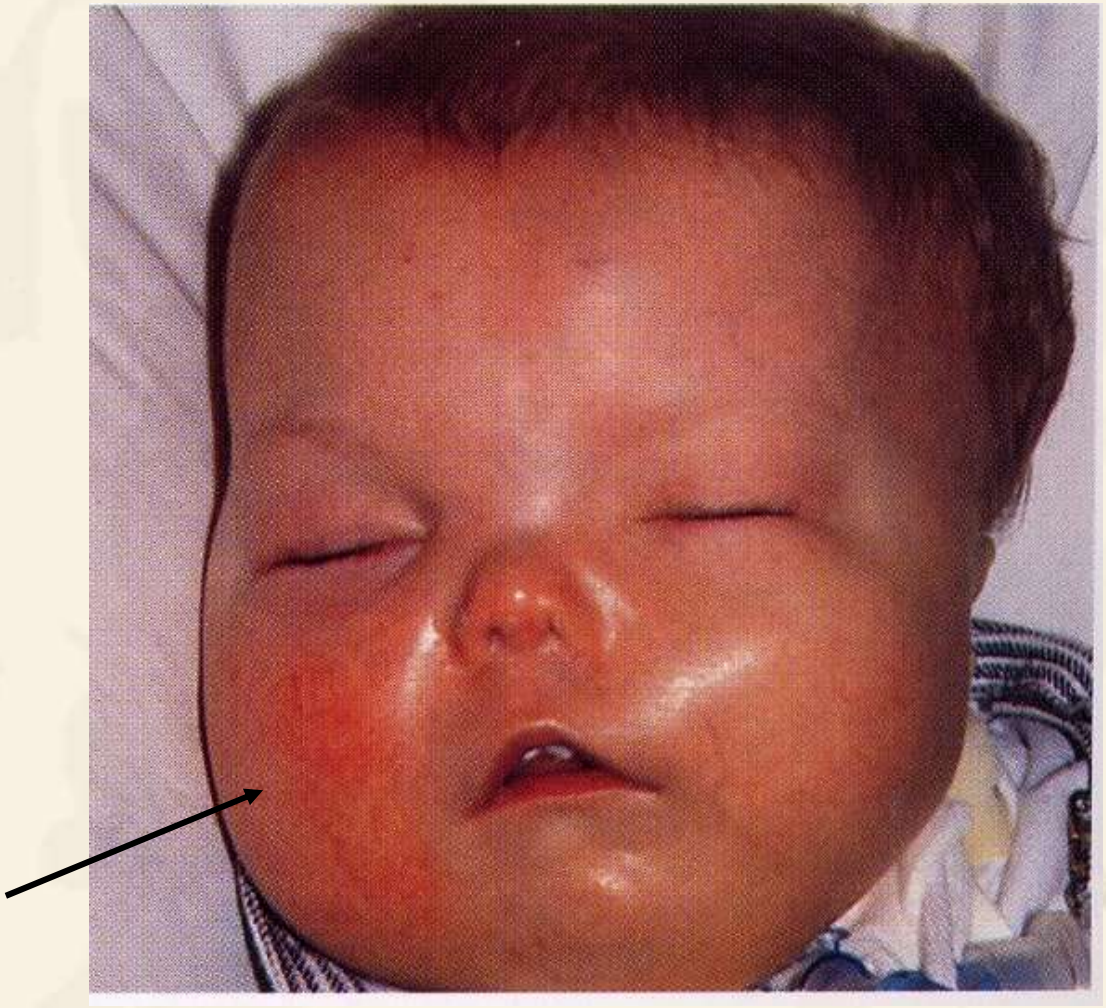


FIGURE 23-4. Anatomic definition of separate lymph node regions used for staging purposes. (Adapted from Kaplan HS, Rosenberg SA. The treatment of Hodgkin's disease. Med Clin North Am 1966;50:1591.)

淋巴結


Preauricular
Postauricular
Suboccipital
Submandibular
Submental
Anterior cervical
Posterior cervical
Supraclavicular
Infraclavicular
Axillary
Epitrochlear
Inguinal
Femoral
Popliteal

右側臉水腫



Pathology in NHL

- Histology subtype,
- Immunophenotype,
- Cytogenetics/oncogenes

1. Lymphoblastic (usually of T-cell origin):
2. Small noncleaved cell lymphoma (SNCCL),

   Burkitt's & non-Burkitt's, B-cell origin):

   t(8;14), t(2;8), t(8;22),
3. Large cell (of T-, or B-, or indeterminate cells origin, rather heterogeneous) one subset: anaplastic large cell lymphoma(ALCL), t(2;5)

Signs & Symptoms in NHL

Vary with **site** and **extent** (correlate with histology subtype)

1. **Lymphoblastic** (usually of T-cell origin): usually a mediastinal mass with dyspnea, chest pain, dysphagia, pleural effusion, or superior vena cava syndrome.
2. **SNCCL**: abdominal tumor, with abdominal pain or distention, bowel obstruction, change in bowel habits, GI bleeding.
3. **LCL**: in many sites, mediastinum, abdomen, bone, soft tissue, skin. CNS is rare

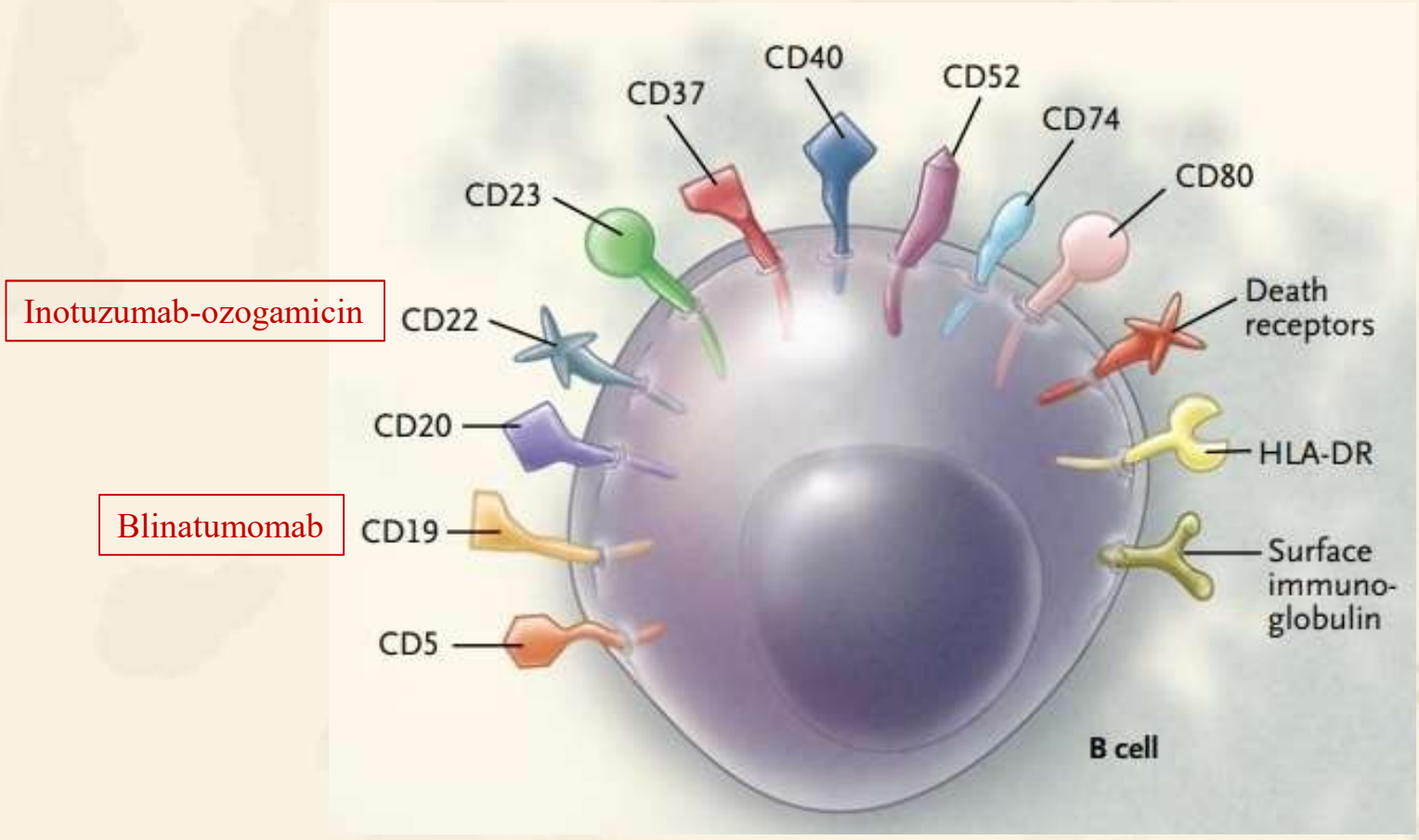
Treatment in NHL

Key: Multiagent chemotherapy (not surgical excision)

For **advanced** NHL: depending on **histologic** subtype

1. **lymphoblastic:** intensive, moderate duration (15-18 mo) & CNS therapy
2. **SNCCL:** intensive, short duration (3-6 mo),
3. **LCL:** rather heterogeneous →controversial, either protocol for lymphoblastic or for SNCCL (only for the B-cell subset of large-cell cases)

B 細胞變異之單株抗體治療選項:
淋巴瘤與慢性淋巴性白血病

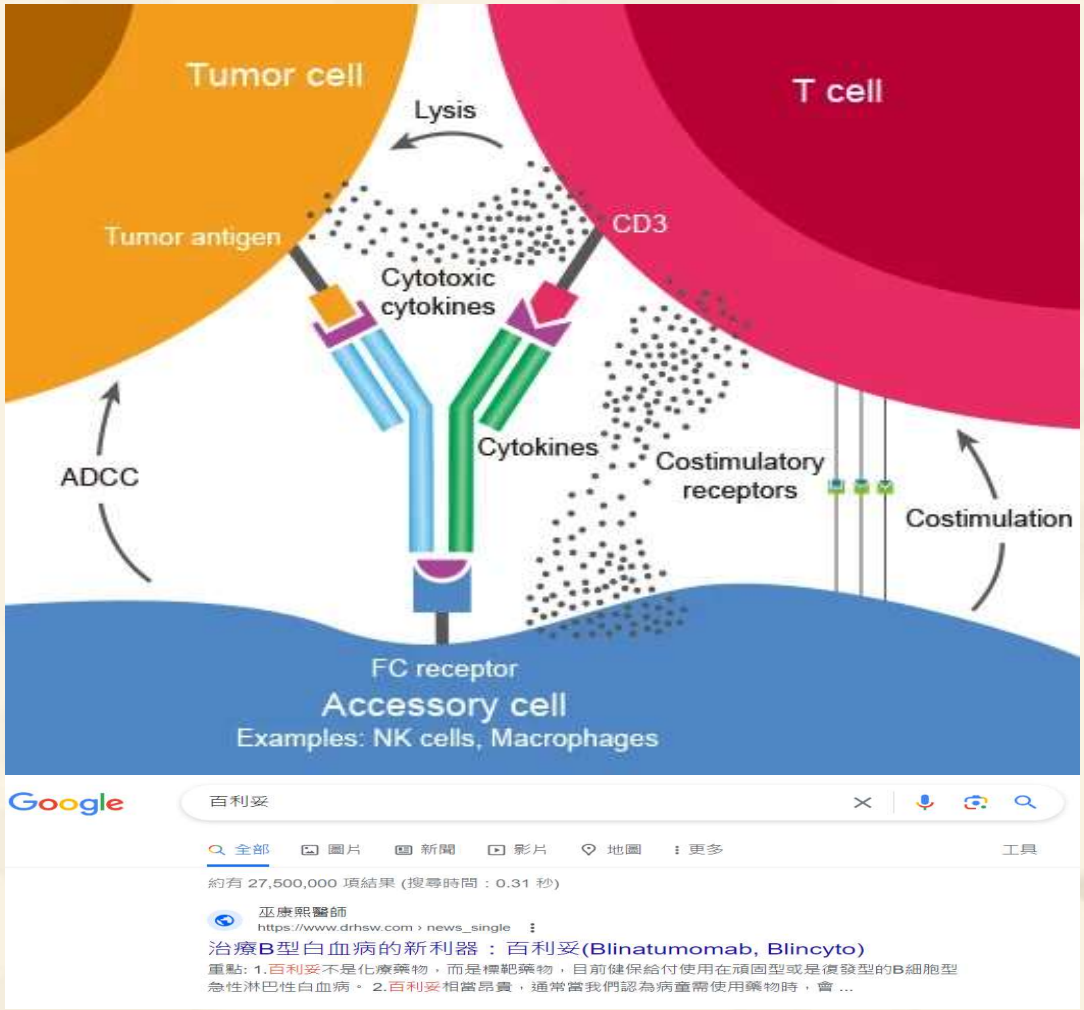


Cheson BD, et al. Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma. N Engl J Med 2008; 359:613-626.
Hiddemann W , Cheson B D, How we manage follicular lymphoma. Leukemia (2014) 28, 1388–1395.

淋巴癌與淋巴性白血病標靶藥物治療

- ◆ 單株抗體療法(多數合併化學治療)
  - ● B 細胞型淋巴癌 (CD 20) ->莫須瘤、
  - ● 何杰金氏淋巴癌/CD30(+)淋巴瘤->雅詩力 (Brentuximab vedotin)
- ◆ 小分子標靶/小分子激酶抑制劑 (多數合併化學治療)
  - ● BTK 抑制劑-> 億科 (Ibrutinib)
  - ● Proteasome 抑制劑-> 萬科 (Bortezomib)
  - ● BCL2 抑制劑->唯可來(Venetoclax)腫瘤壞死症候群與骨髓抑制毒性
- ◆ 免疫治療: 雙特異抗體治療 (BiTe)、Checkpoint 抑制劑、嵌合抗原受體T细胞 (CART) 治療

Bispecific Antibodies for hematologic malignancies (B-lymphocyte: CD3-CD19: Blinatumomab 百利妥)



細胞治療

1. 細胞治療
2. 幹細胞治療

   # 造血幹細胞治療(骨髓移植):
   過程、併發症、半吻合移植、
   治療血液以外的病

   # 臍帶血和臍帶血移植

   # 間質幹細胞:從基礎到臨床
3. CAR-T 治療: 個案分享和原理

什麼是細胞/幹細胞治療?

- 用(人類)的細胞來治療疾病或受傷的組織，

  如紅血球治療貧血

- 造血幹細胞(骨髓移植)是用得最久的幹細胞治療

- (幹)細胞可分泌許多的物質來修復受傷的組織，

  是細胞治療很好的來源

- 自體 VS 異體

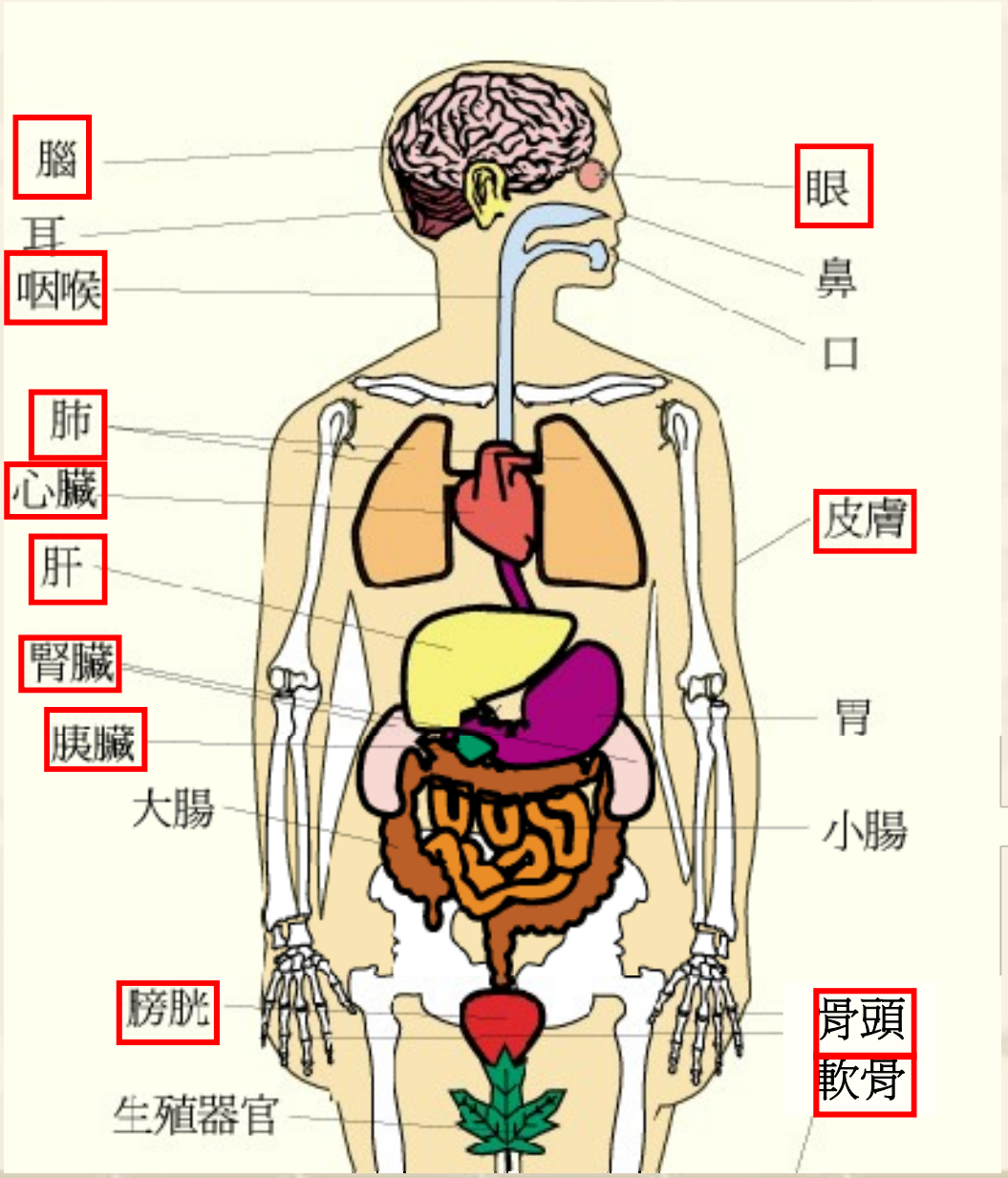
Several issues in cell therapy(1)

- What disease is treated?
- Who / When should cells be transplanted?
- Which kind of cell is suitable?
- What is the route of administration?
- What is the appropriate cell dosage?

Several issues in cell therapy(2)

- Give other treatments?
- How to evaluate the effect?
  Image? Tests? Others?
- **Safety Consideration!!! Most important!!!**
- What is the ideal mechanism of action of stem cells
- Government regulation of cell therapy

以細胞修復受傷的組織或器官



幹細胞的真和假

- 2005年12月: 韓國克隆之父黃禹錫幹細胞克隆造假
- 2015年11月: 日本居里夫人小保方晴子 PS 出可分化為多種細胞的「STAP 萬能細胞」
- 2018年10月: 31篇論文驚爆造假: 哈佛專家「心肌可再生」影響一代人
- 再生醫療/幹細胞的專家??? 冰山一角，以管窺天!

Which kind of cell is suitable

1. Hematopoietic stem cells (HSCs):

   haploidentical HSCT

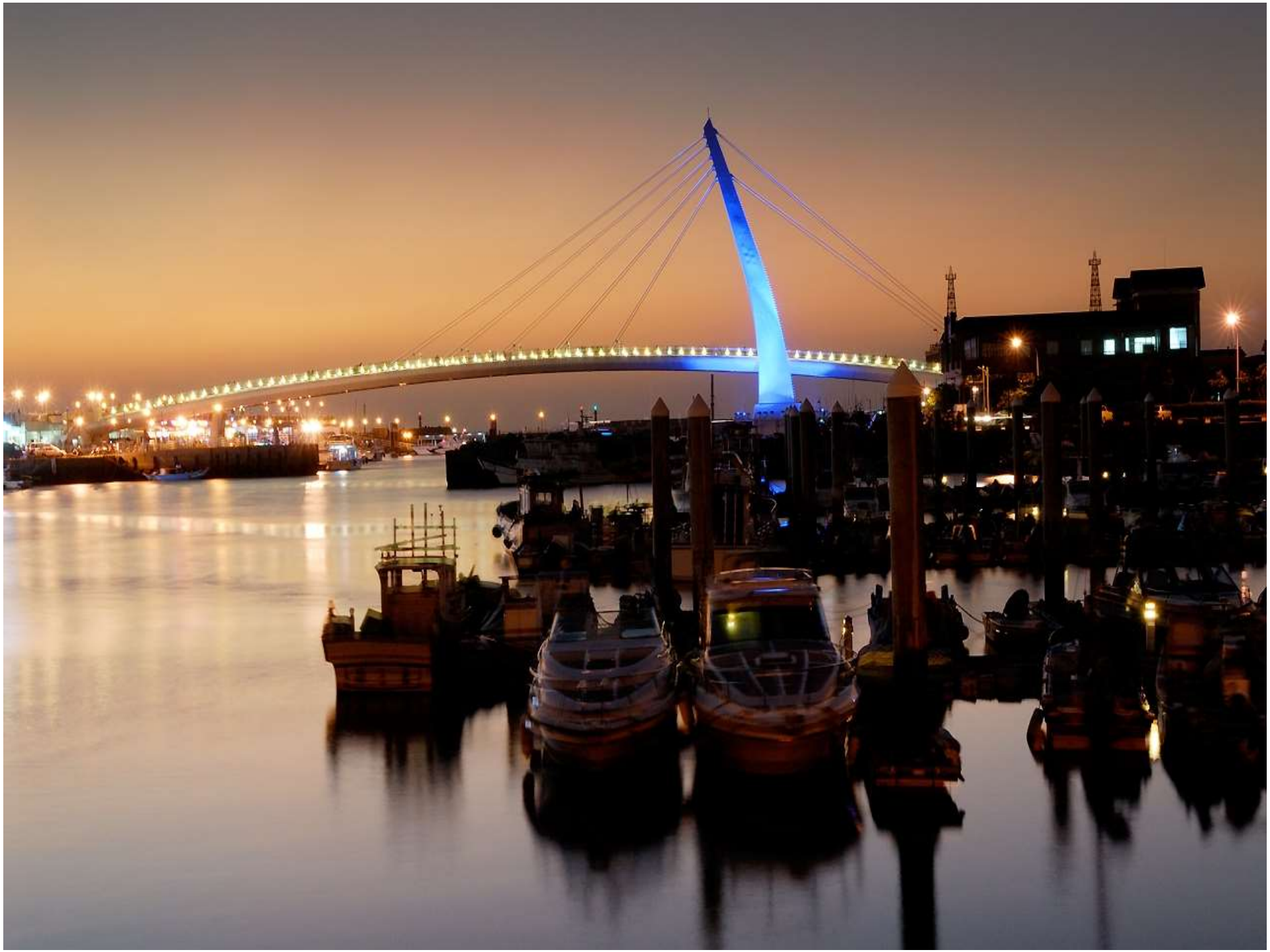
   CD34+ cells teat stroke, critical limb (特管法)

2. Mesenchymal stem cells (MSCs)

3. Cells therapy for cancer:

   T cell, NK cell, DC, CAR-T

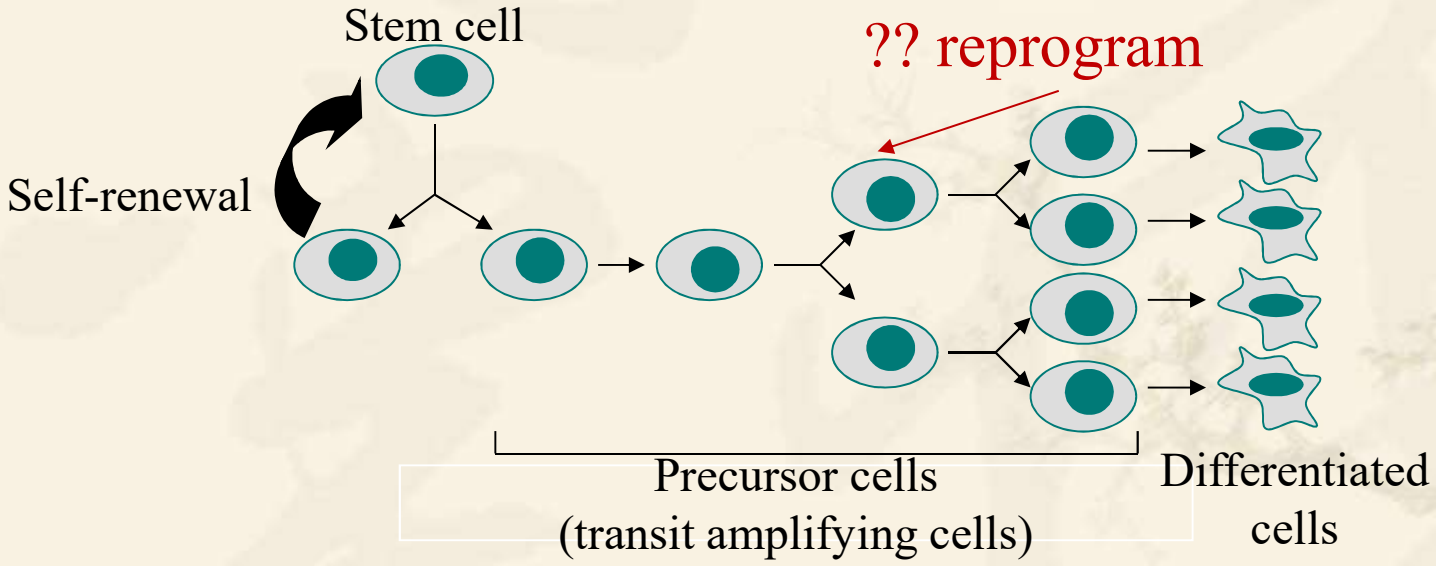
4. Others



Definition of stem cells

- Stem cells

  --An undefferentiated cell capable of producing daughter cells that can either remain a stem cell (self-renewal/proliferation) or commit to a pathway (differentiation)



最臨床的幹細胞應用
Hematopoietic Stem Cell Transplantation
(Bone marrow transplantation 骨髓移植)

Thomas因骨髓移植於1957獲諾貝爾獎

HSC Transplantation

(I). Pretransplant Considerations

(II). Transplant Procedure

(III). Transplant-Related Problems

(IV). Long-Term Follow-up

(I). Pretransplant Consideration

1. **Rationale and Indications for HSCT**
2. **Timing of Transplantation (選好病人)**
3. **Stem Cell Sources (選好細胞/捐者)**

Rationale of HSCT

1. **Hematopoietic rescue (myelosuppression):**

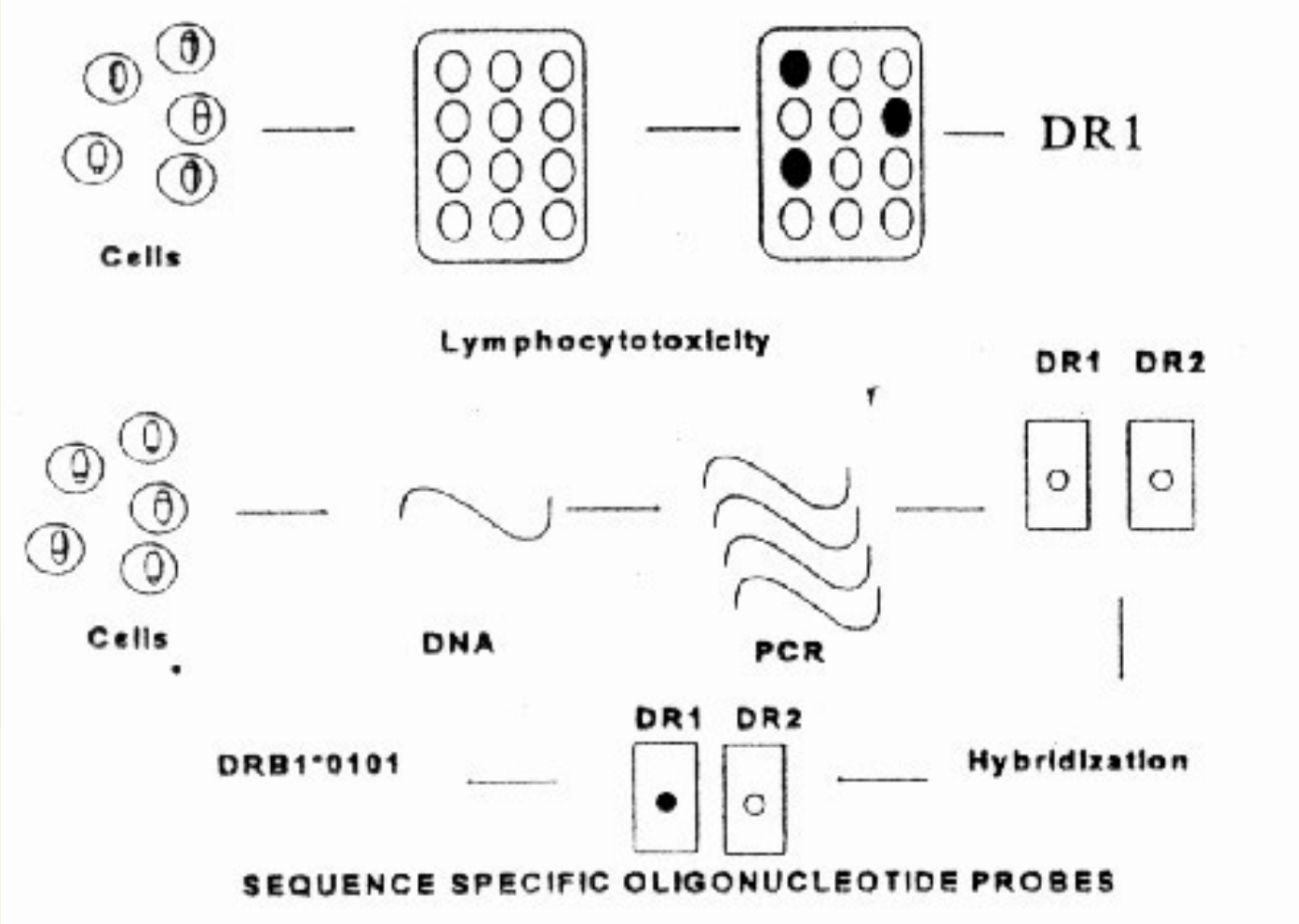
   Autologous HSCT

2. **Replacement (Hematopoietic or immunological):**

   Allogeneic HSCT

3. **Others**

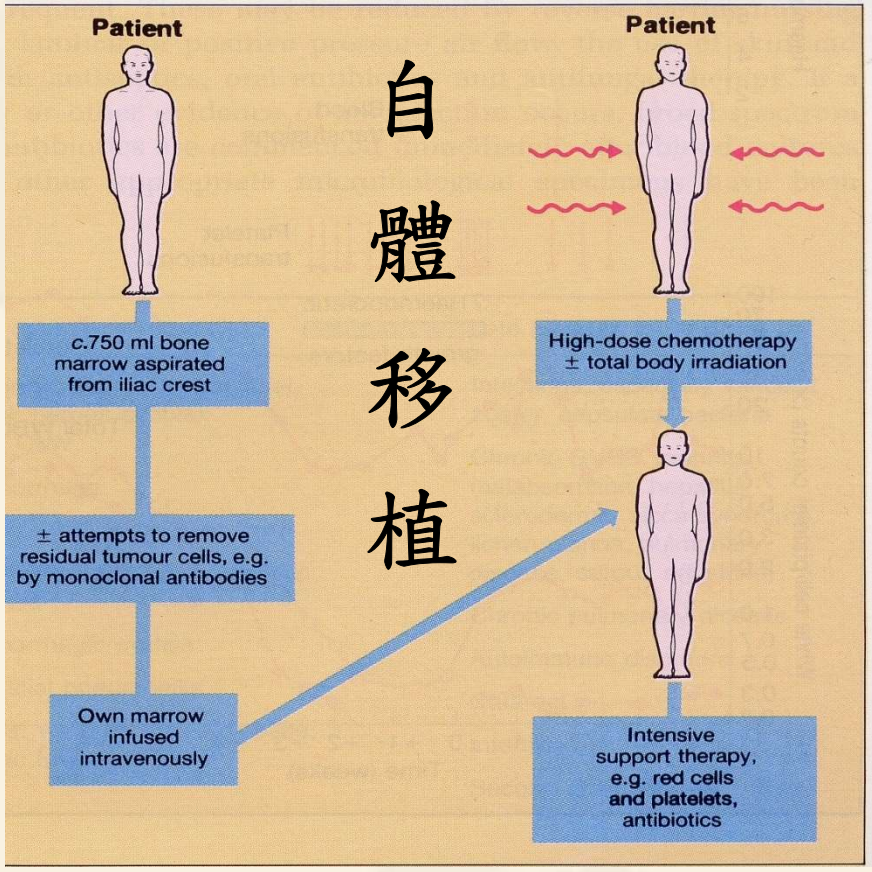
HLA typing

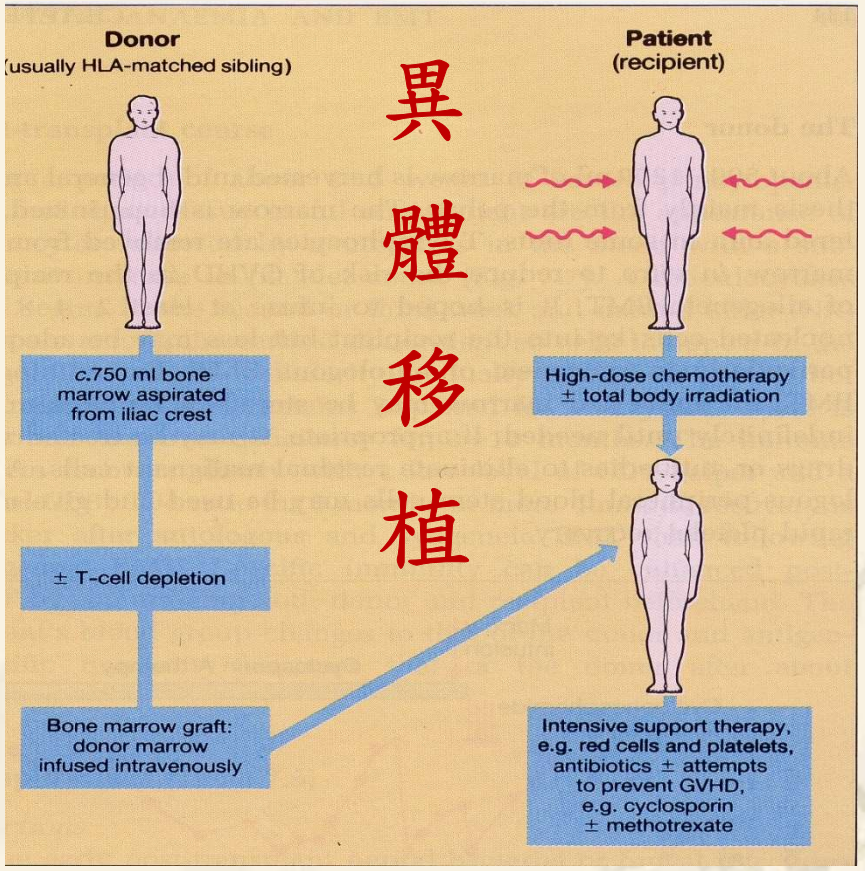

DR1
Cells
Lymphocytotoxicity
DR1 DR2
Cells
DNA
PCR
DR1 DR2
DRB1*0101
Hybridization
SEQUENCE SPECIFIC OLIGONUCLEOTIDE PROBES

(II). Transplant Procedure

1. **Conditioning (preparative) Regimens**
2. **Collection and Processing of Stem Cells**
3. **Infusion of HSCT**

自體骨髓移植 vs 異體骨髓移植





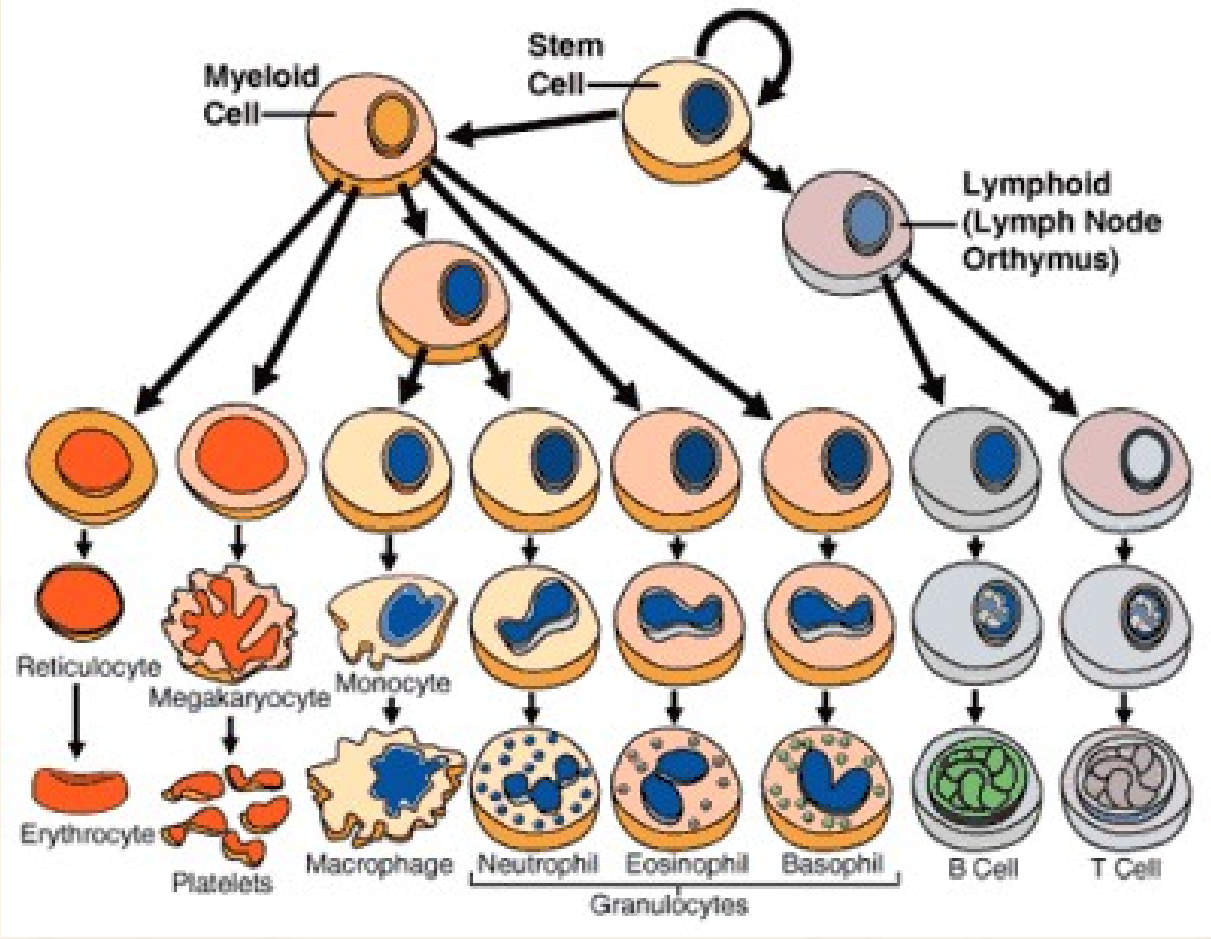
(II).1: Definition of conditioning

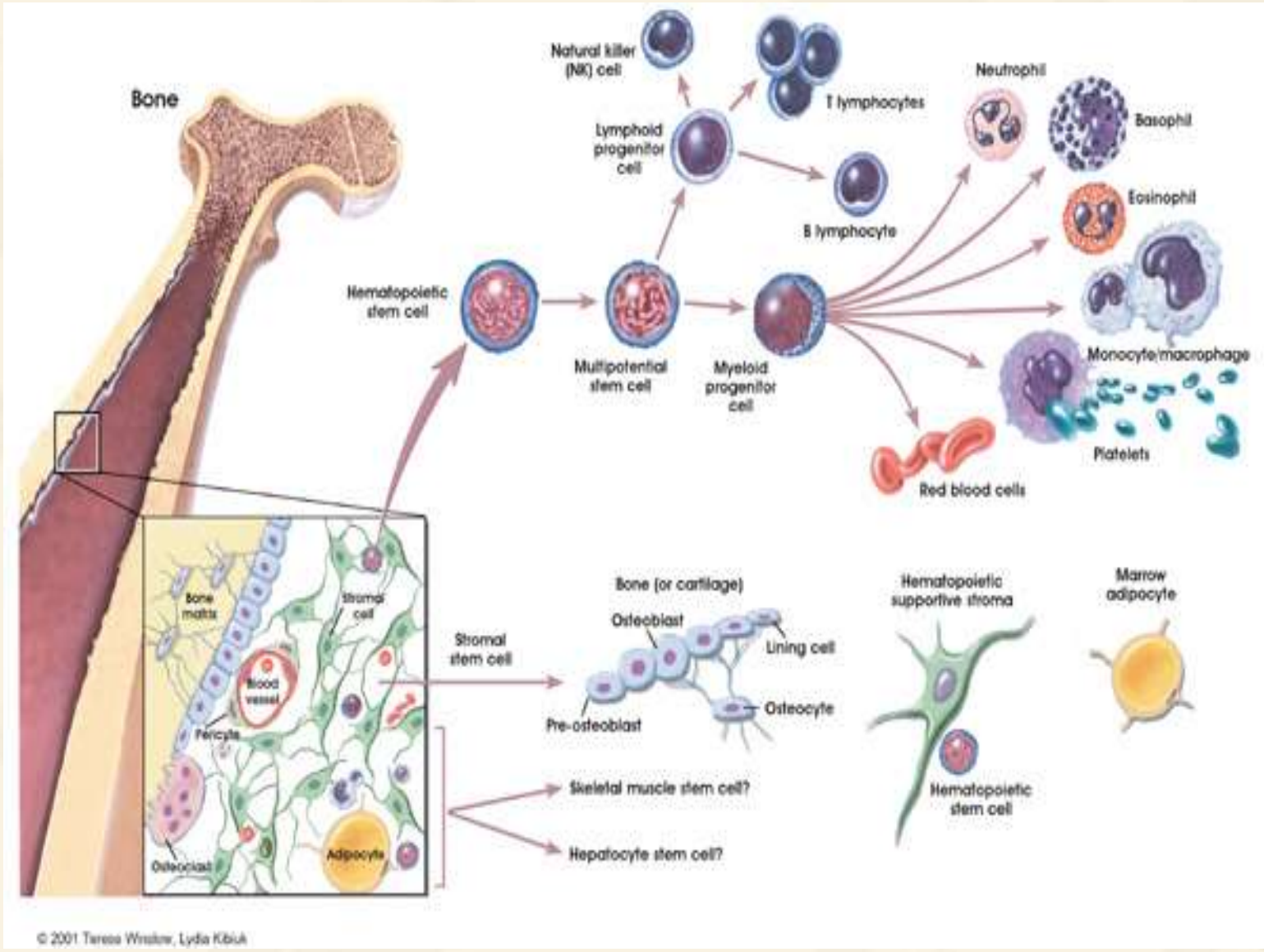
Conditioning is the preparative regimen administered to the patients undergoing HSCT before HSCT

The pre-HSCT conditioning had to:

1. Eradicate the malignancy
2. Provide sufficient immunosuppressive to ensure engraftment and to prevent both rejection and GVHD.
3. Provide stem cell niches in the host BM for the new stem cells.

(II).2: Hematopoietic stem cells: self-renew and differentiation




Bone
Natural killer (NK) cell
T lymphocytes
Lymphoid progenitor cell
B lymphocyte
Neutrophil
Basophil
Eosinophil
Monocyte/macrophage
Platelets
Red blood cells
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Bone matrix
Stromal cell
Blood vessel
Pericyte
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte
© 2001 Teresa Winslow, Lydia Kibiuk

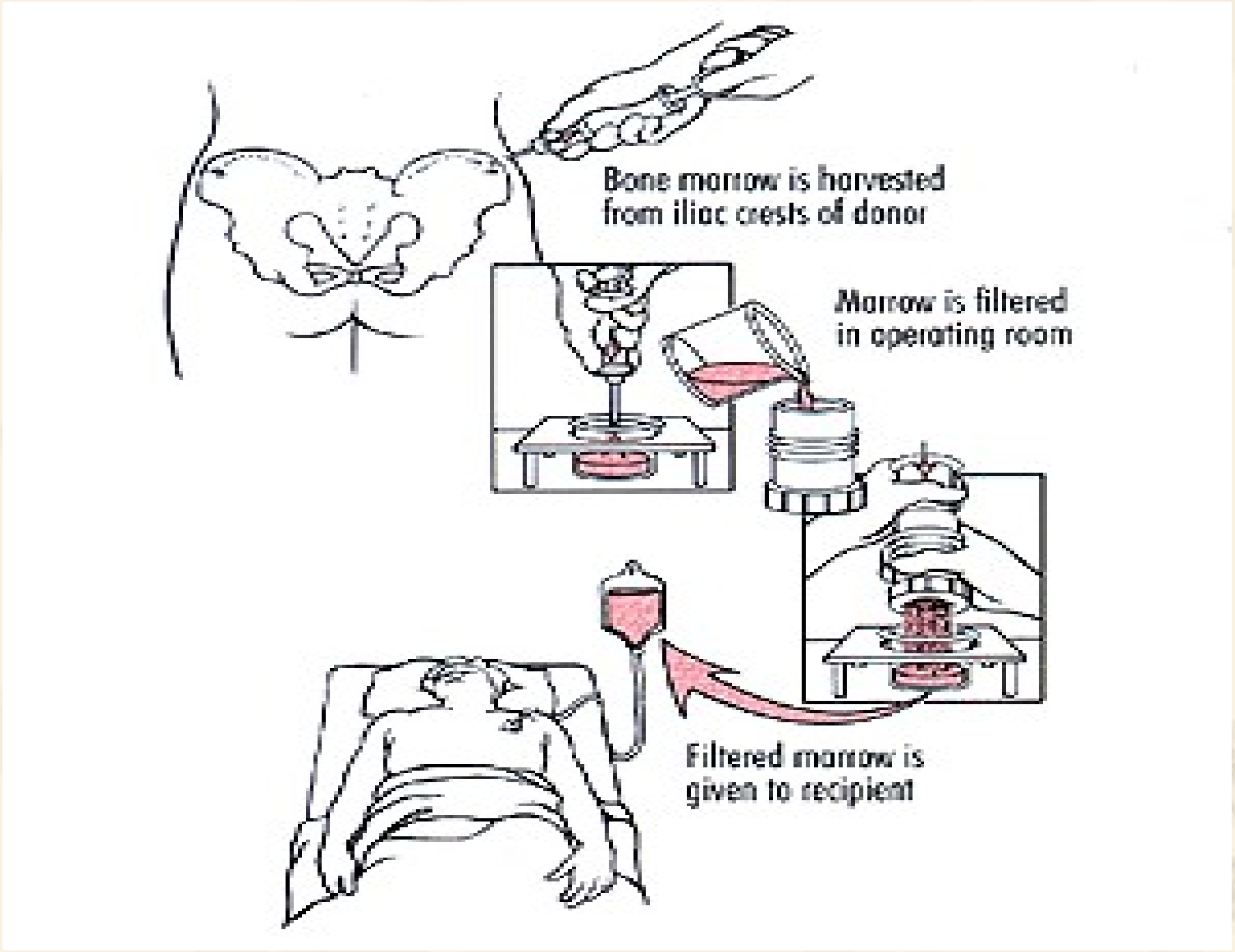
HSC Sources and Donors

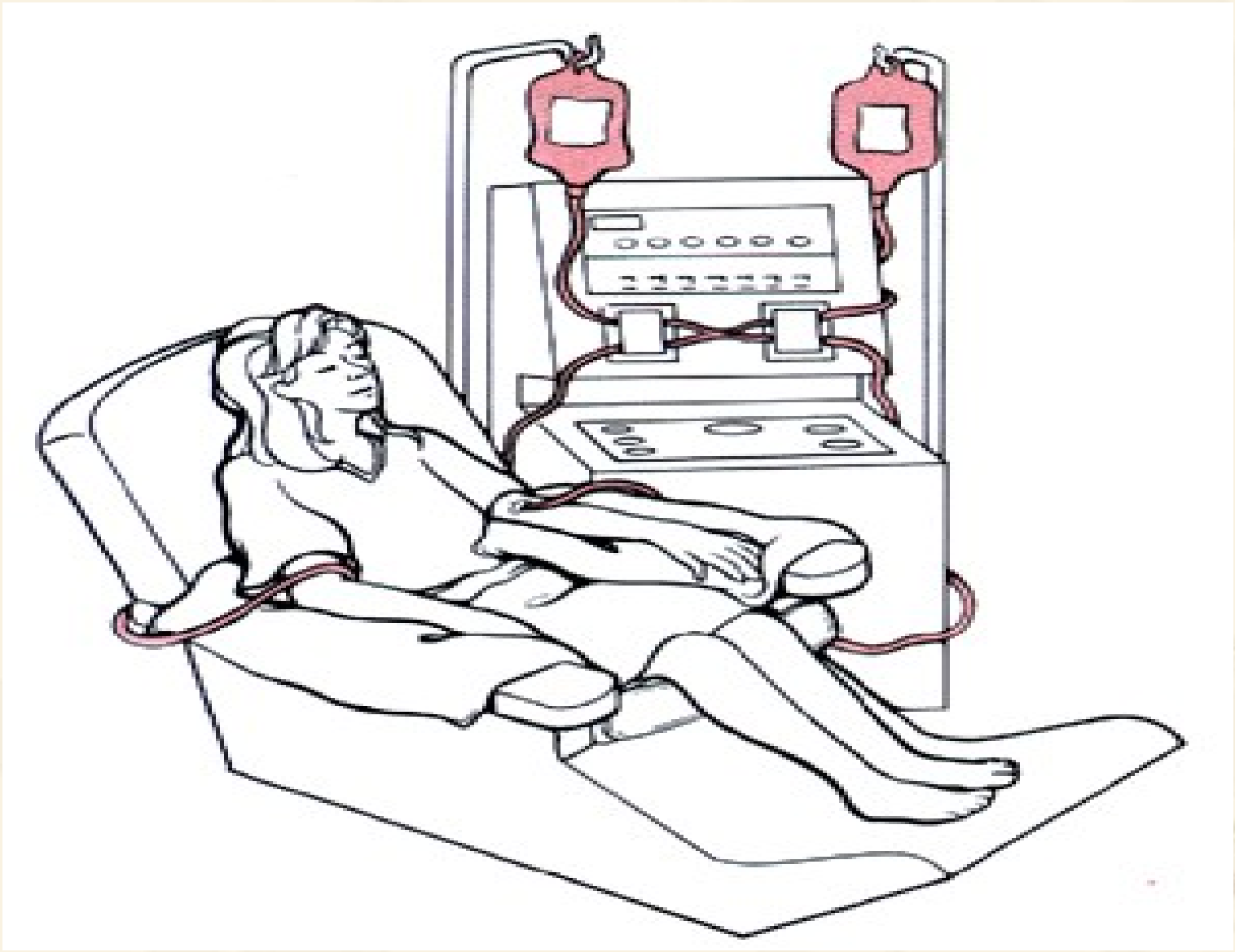
- Bone Marrow (MB)
- Peripheral Blood Stem Cell (PBSC)
- Umbilical Cord Blood (UCB)
- Others (fetal liver)

Autologous

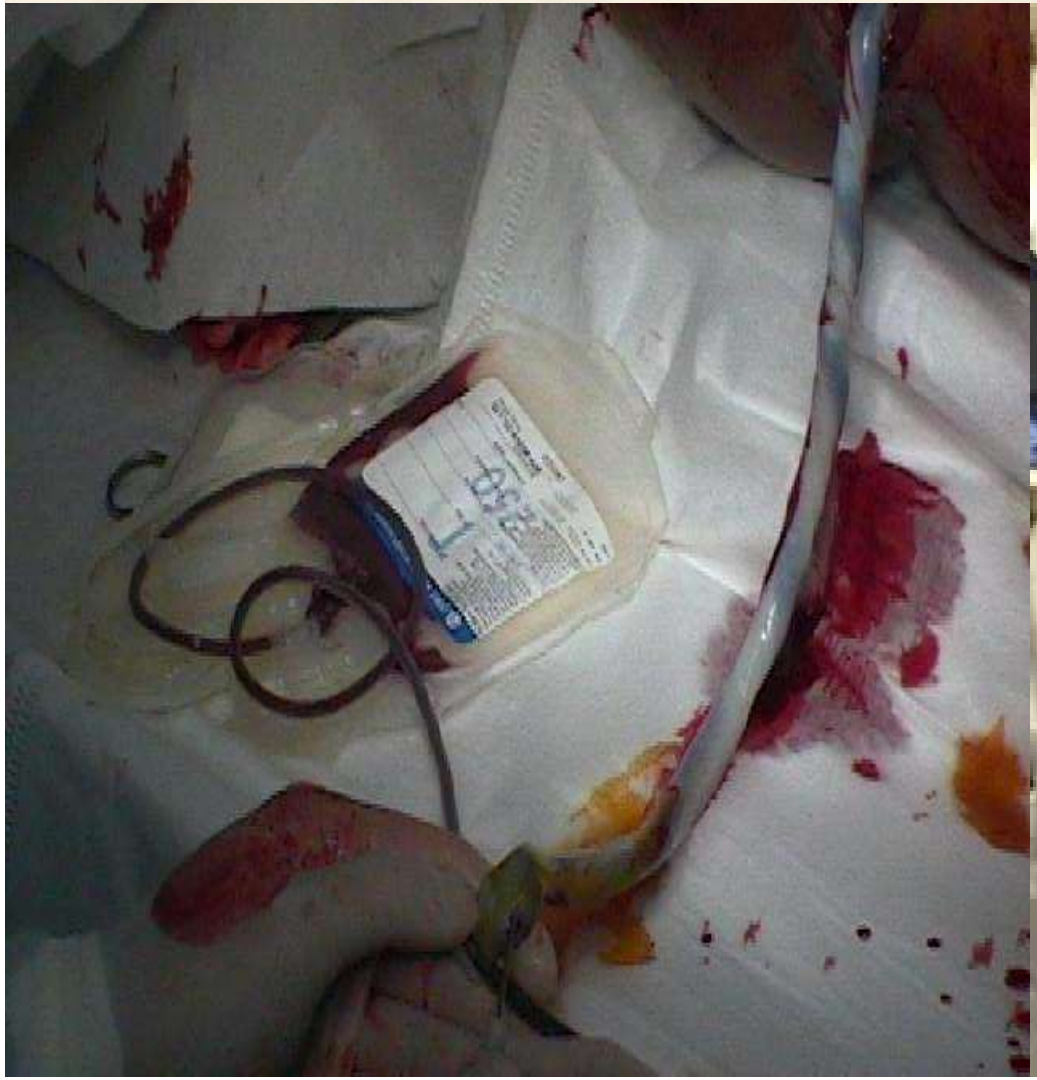
Allogeneic:

1. Sibling
2. match unrelated donor (MUD)
3. mismatch match unrelated donor (MMUD)
4. Haploidentical


Bone marrow is harvested
from iliac crests of donor
Marrow is filtered
in operating room
Filtered marrow is
given to recipient



臍 帶 血 的 收 集



Stem cell storage and infusion

- Cryopreservation:

  addition: DMSO; storage -196°C

- Thawing and Infusion:
  - once thaw (40°C), direct and rapid infusion via central access, no more than 15 (30) minutes
  - side effect: volume overload, bradycardia, nausea/vomiting, fever, tachycardia, hypo/hypertension, allergic reaction
  - prevention: volume reducing, antimetics, diphenhydramine, steroid,

    remove DMSO prior infusion (?)

III. Transplant-Related Problems

1. Side Effects of Conditioning Regimens
2. Graft Failure
3. Graft-Versus-Host Disease
4. Management of Infection
5. Single and Multi-Organ Failure
6. Chronic Graft-Versus-Host Disease
7. Delay Complication

Regimen Related Toxicity- First 30 Days
Early Toxicity of High-Dose Therapy

- Pancytopenia: infection and blood transfusion
- Cardiac: marrow infusion, cyclophosphamide
- Hepatic: veno-occlusive disease (VOD)
- GI Toxicity: nausea/vomiting, diarrhea, mucositis
- Pulmonary: infection, diffuse alveolar hemorrhage, idiopathic interstitial peumonitis
- Hemorrhagic cystitis: prophylaxis: hydration, diuretics, MESNA
- Renal: drugs, secondary to cardiovascular problems
- Nervous: metabolic, leukoencephalopathy, drug, infection, hemorrhage

Veno-Occlusive Disease (VOD)

- Etiology: secondary to liver damage from high-dose chemotherapy and radiation
- Prophylaxis: heparin
- Therapy:
  - essentially supportive
  - low-dose tissue plasminogen activator
  - others: high-dose steroid
  - defibrotide

【民視異言堂】義肢女孩向前走

YouTube · 民視讚夯 Formosa TV Thumbs Up · 2023年8月14日

Relationship between time of HSCT and organisms causing important infections

Period of Neutropenia (Day 0-30)	Period of Acute GVHD (Day 30-100)	Period of Chronic GVHD (Day >100)
Gram negative bacteria	Gram negative bacteria	Encapsulated bacteria
gram positive bacteria	Gram positive bacteria	Varicella zoster
Herpes simplex	CMV-Cytomegalovirus	Pneumocystis carinii
Candida spp.	BK virus	Aspergillus spp.
Aspergillus spp.	EB virus	
	Varicella zoster	
	Candiada spp.	
	Aspergillus spp.	
	Pneumocystic carinii	
	Toxoplasma gondii	

精準的檢驗是骨髓移植的成功關鍵之一

1. preemptive treatment : 早期發現感染，在發病前給需治療: EBV, CMV, Aspergillus galactomannan antigen
2. Bacteria, fungus的藥物敏感性: 抗藥性的產生(ESBL, VRE, CRAB…)
3. 臨床藥物治療監測Therapeutic Drug Monitoring(TDM): CsA, tacrolimus, sirolimus, voroconazole… 因Drug-Drug interaction，非常重要!

Infection in HSCT

Changes of serum aspergillus galactomannan during hematopoietic stem cell transplantation in children with prior invasive aspergillosis

Te-Fu Weng[1†], Kang-Hsi Wu[1,2†], Han-Ping Wu[3,4], Ching-Tien Peng[1,5] and Yu-Hua Chao[6,7*]

Successful treatment of disseminated mixed invasive fungal infection after hematopoietic stem cell transplantation for severe aplastic anemia

Weng T-F, Ho M-W, Lin H-C, Lu M-Y, Peng C-T, Wu K-H. Successful treatment of disseminated mixed invasive fungal infection after hematopoietic stem cell transplantation for severe aplastic anemia. Pediatr Transplantation 2012: 16: E35–E38. © 2010 John Wiley & Sons A/S

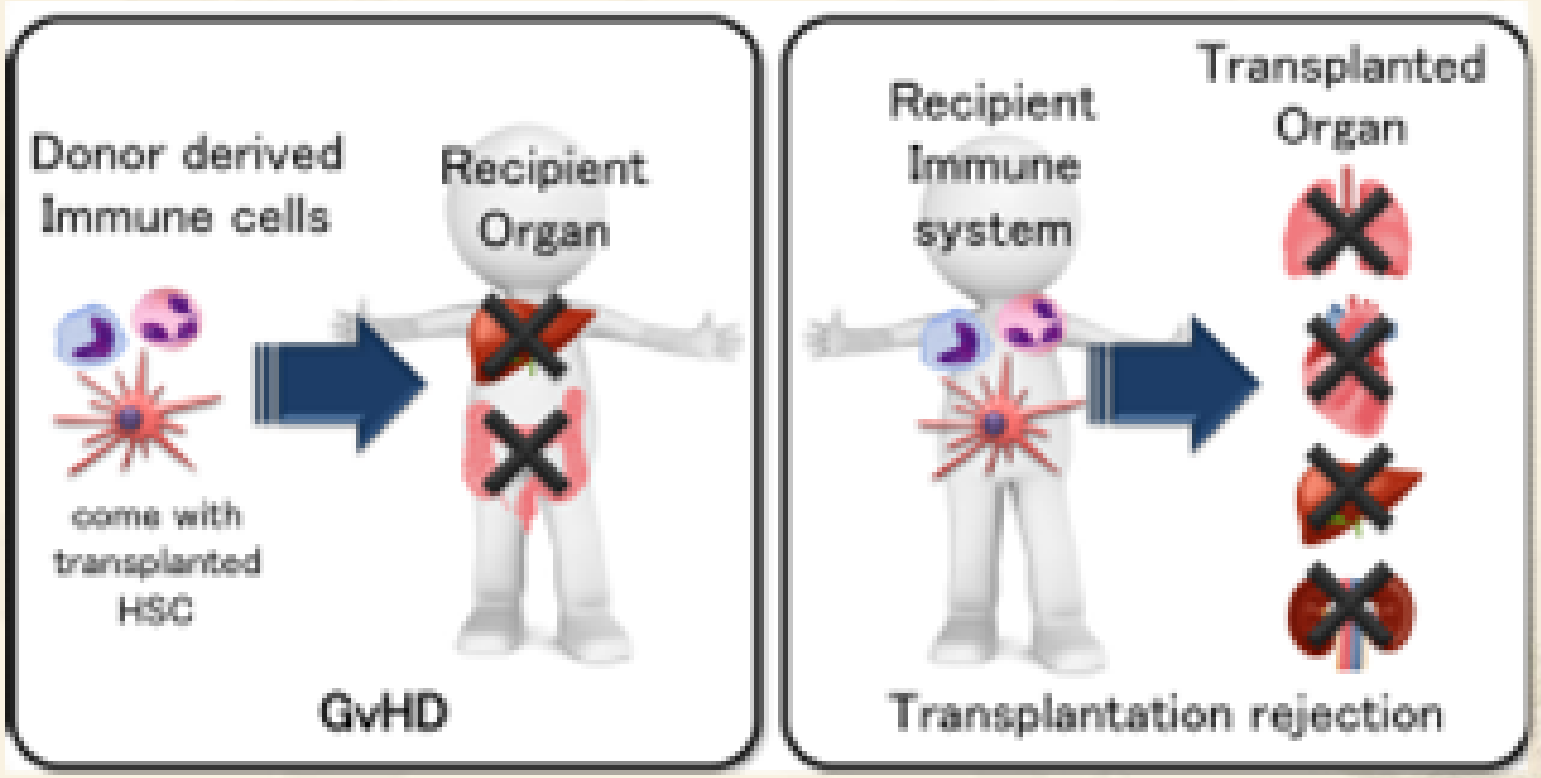
Te-Fu Weng[1], Mao-Wang H… Chuan Lin[1], Meng-Yao Lu[3], … Peng[1,4] and Kang-Hsi Wu[1]
Departments of [1]Pediatrics and [2]Intern… China Medical University Hospital, Tai…

EFFECTIVE TREATMENT OF SEVERE BK VIRUS-ASSOCIATED HEMORRHAGIC CYSTITIS WITH LEFLUNOMIDE IN CHILDREN AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

A PILOT STUDY

Kang-Hsi Wu, MD,† Tefu Weng, MD,†*

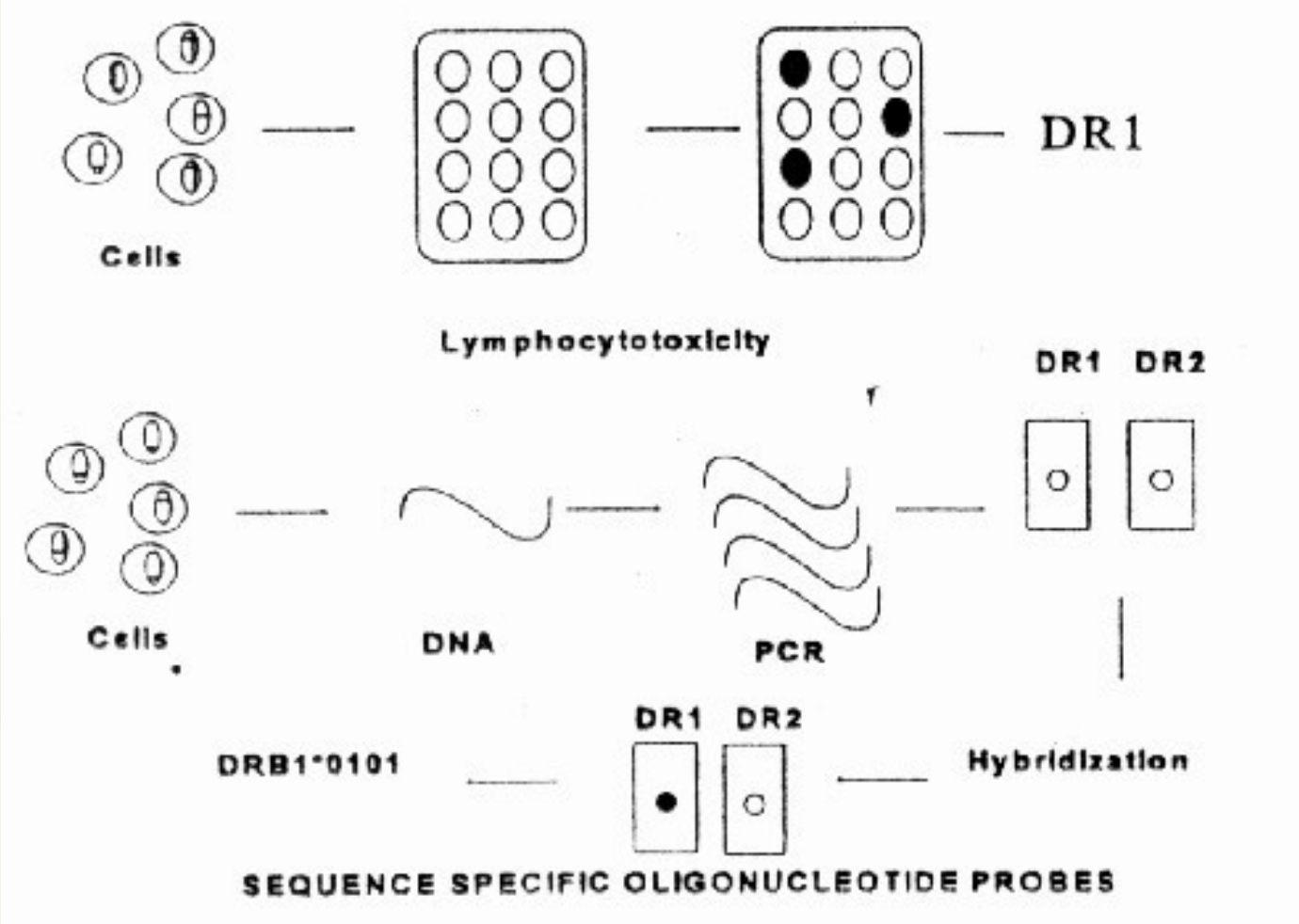
造血幹細胞移植的惡夢:
Graft-versus-host disease (移植物抗宿主疾病)



Advance in HSCT (from 2005)

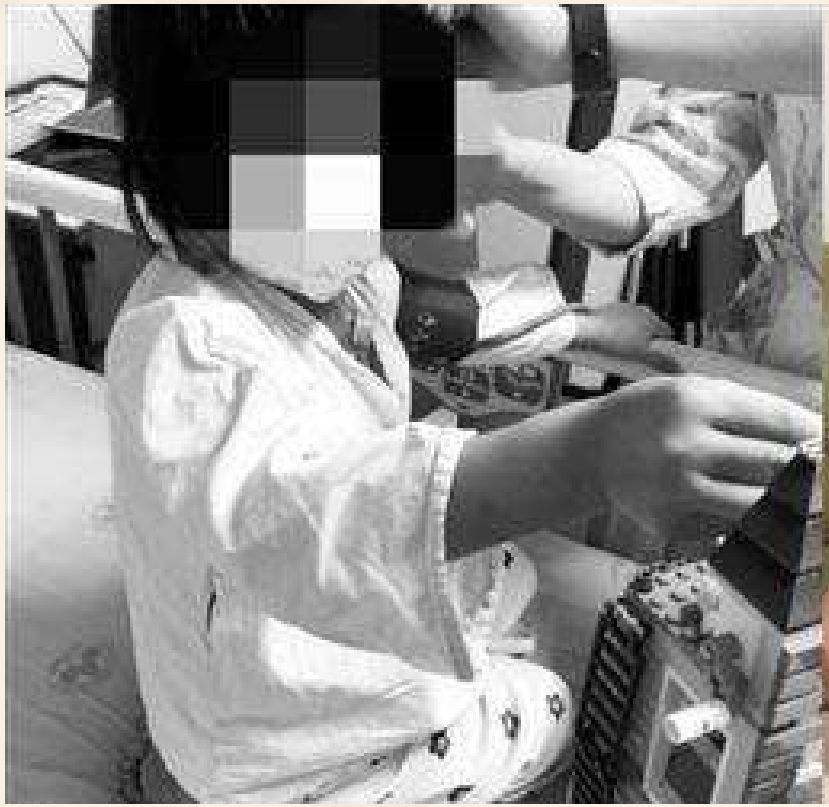
- Reduced-intensity HSCT
- Umbilical cord blood bank/ transplantation
- Haploidentical donors
- In vitro expansion of stem cells
- More efficacious purging
- Intrauterine HSCT
- More efficacy and less side effect to control GVHD
- More efficacy to control CMV
- Genetic manipulation of HSC (Nature, Science, NEJM)
- Control stem cells

HLA typing


DR1
Cells
Lymphocytotoxicity
DR1 DR2
Cells
DNA
PCR
DR1 DR2
DRB1*0101
Hybridization
SEQUENCE SPECIFIC OLIGONUCLEOTIDE PROBES

等骨髓救命　5歲血癌童：想長大

新聞 2020年05月09日




台視新聞HD
不必等配對！
「半吻合」骨髓移植救血癌男童

什麼是半吻合(haploidentical)骨髓移植

- 目前骨髓移植大多不用抽骨髓，而是用周邊造血幹細胞來做移植，所以也稱造血幹細胞移植。
- 而血癌通常做**異體**的骨髓移植，異體的骨髓移植需要配對，有時會找不到吻合度適合的捐者。
- 近年來由父母提供造血幹細胞的半吻合造血幹細胞移植，且因捐者是父母，所以幾乎不會有找不到捐贈者的問題，且可快速執行移植。
- 這種移植方式困難度較高，如為了減少排斥的問題，會使用**較高的免疫抑制藥物**，這將增加感染的併發症。

半吻合骨髓移植常見嚴重的併發症

1. 植入失敗：一般半吻合骨髓移植，成功植入率約90%，我們團隊成功植入率為100%。
2. 移植物抗宿主疾病：一般半吻合骨髓移植，嚴重抗宿主疾病為20-40%，我們團隊為0%。
3. 移植後感染：半吻合移植後感染率相當的高，我們團隊都一一克服，沒有病患因感染而造成死亡。

pharmaceuticals

MDPI

Article

Antithymocyte Globulin Plus Post-Transplant Cyclophosphamide Combination as an Effective Strategy for Graft-versus-Host Disease Prevention in Haploidentical Peripheral Blood Stem Cell Transplantation for Children with High-Risk Malignancies

Kang-Hsi Wu [1,2], Te-Fu Weng [1], Ju-Pi Li [1,3] and Yu-Hua Chao [1,2,4,*]

這是全世界第一篇，在兒童半吻合造血幹細胞移植時，使用「抗胸腺細胞免疫球蛋白」(ATG) 加上「移植後環磷醯胺」(PTCy)，預防兒童移植物抗宿主疾病(GVHD)的發生，100%成功植入(engraftment)，沒有一位病患死於移植物抗宿主疾病(GVHD)

當我們的先進治療被國外證明時

Haploidentical peripheral blood stem cell transplantation with posttransplant cyclophosphamide in a child with neuroblastoma relapse after autologous peripheral blood stem cell transplantation. Pediatr Blood Cancer. 2022 Feb

我們團隊，界世第一例，使用半吻合造血幹細胞，成功治療自體造血幹細胞移植後，復發的惡性神經母細胞瘤

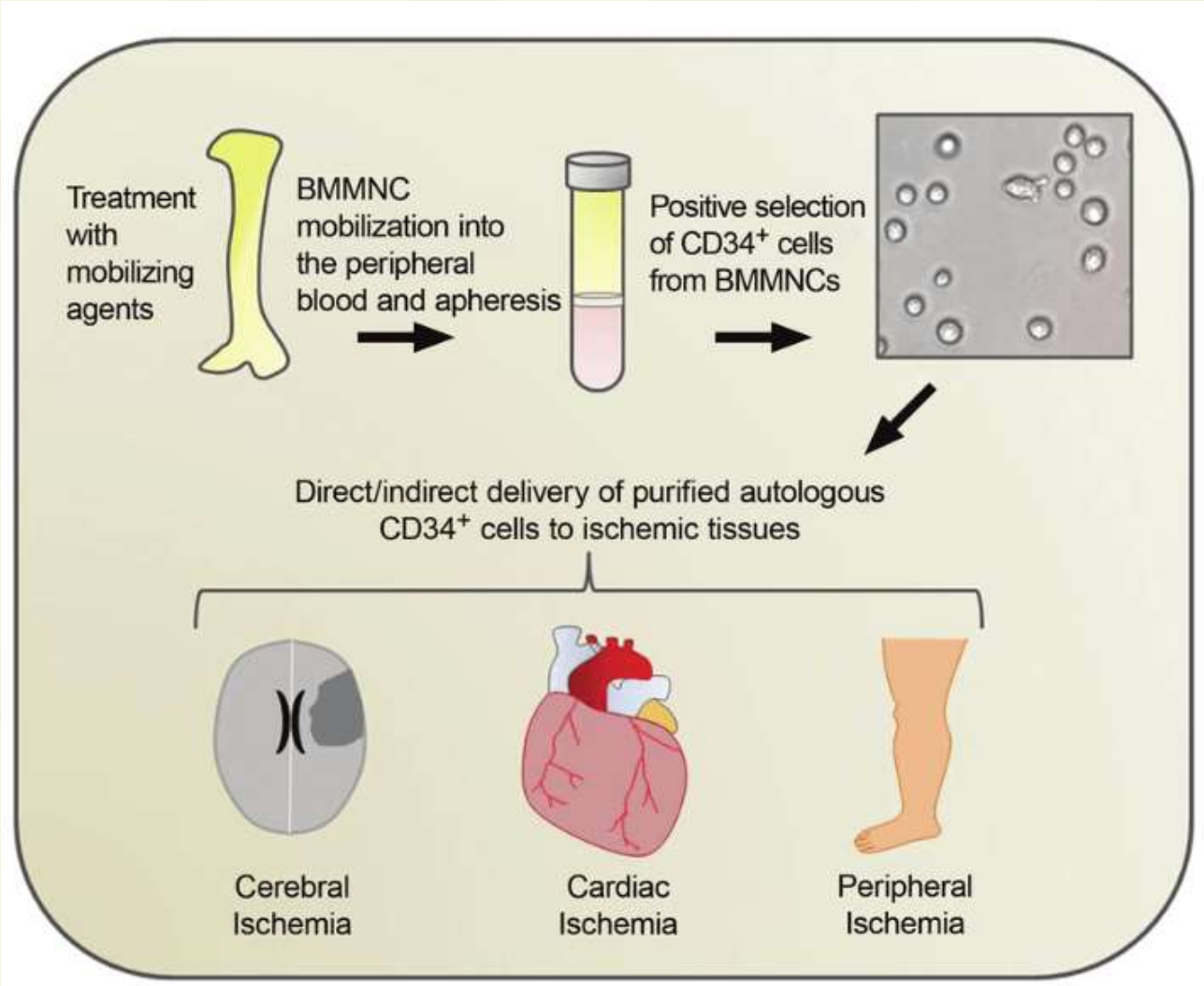
Anti-GD2 Antibody Dinutuximab Beta and Low-Dose Interleukin 2 After Haploidentical Stem-Cell Transplantation in Patients With Relapsed Neuroblastoma: A Multicenter, Phase I/II Trial. J Clin Oncol. 2023 Jun 10;41(17):3135-3148.

愛女嗜血症候群命危 父急捐髓救命 半吻合骨髓移植世界首例成功

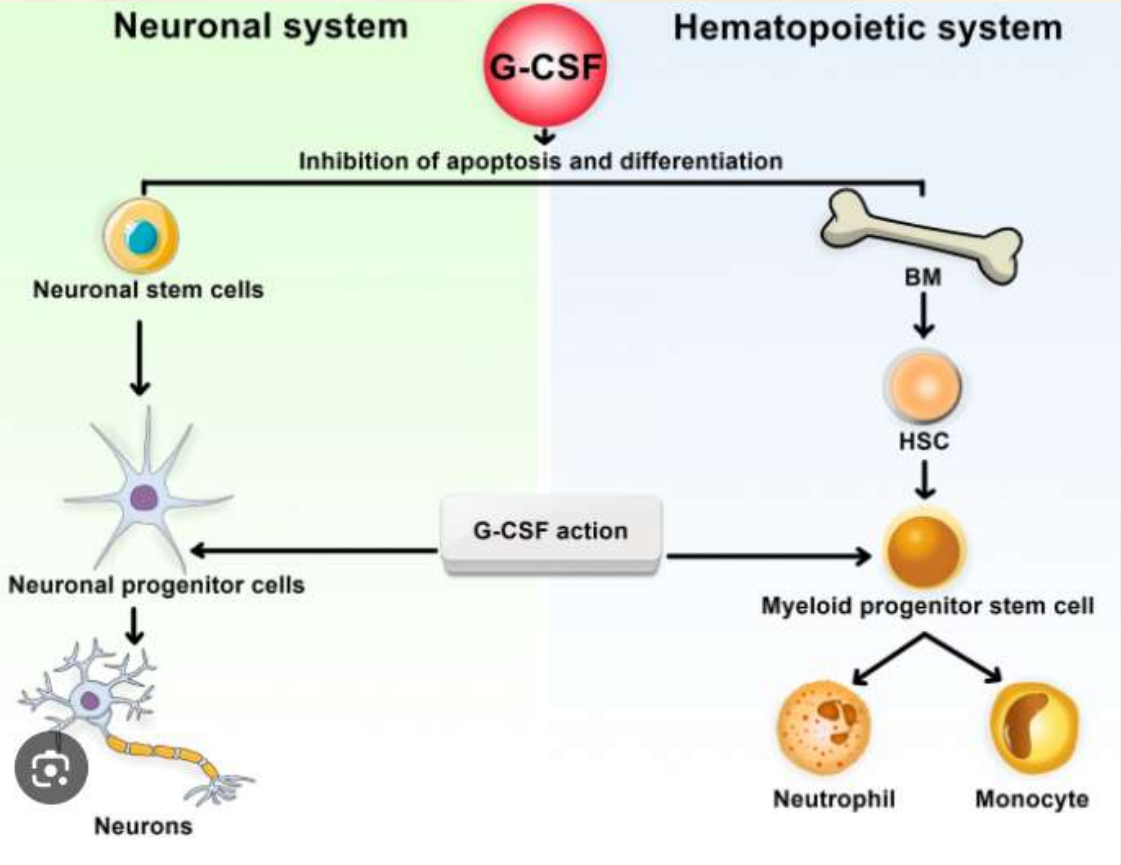
2022/10/18 16:25


@HUCAPTURES

週邊造血幹細胞(CD34+)治療血液以外的疾病

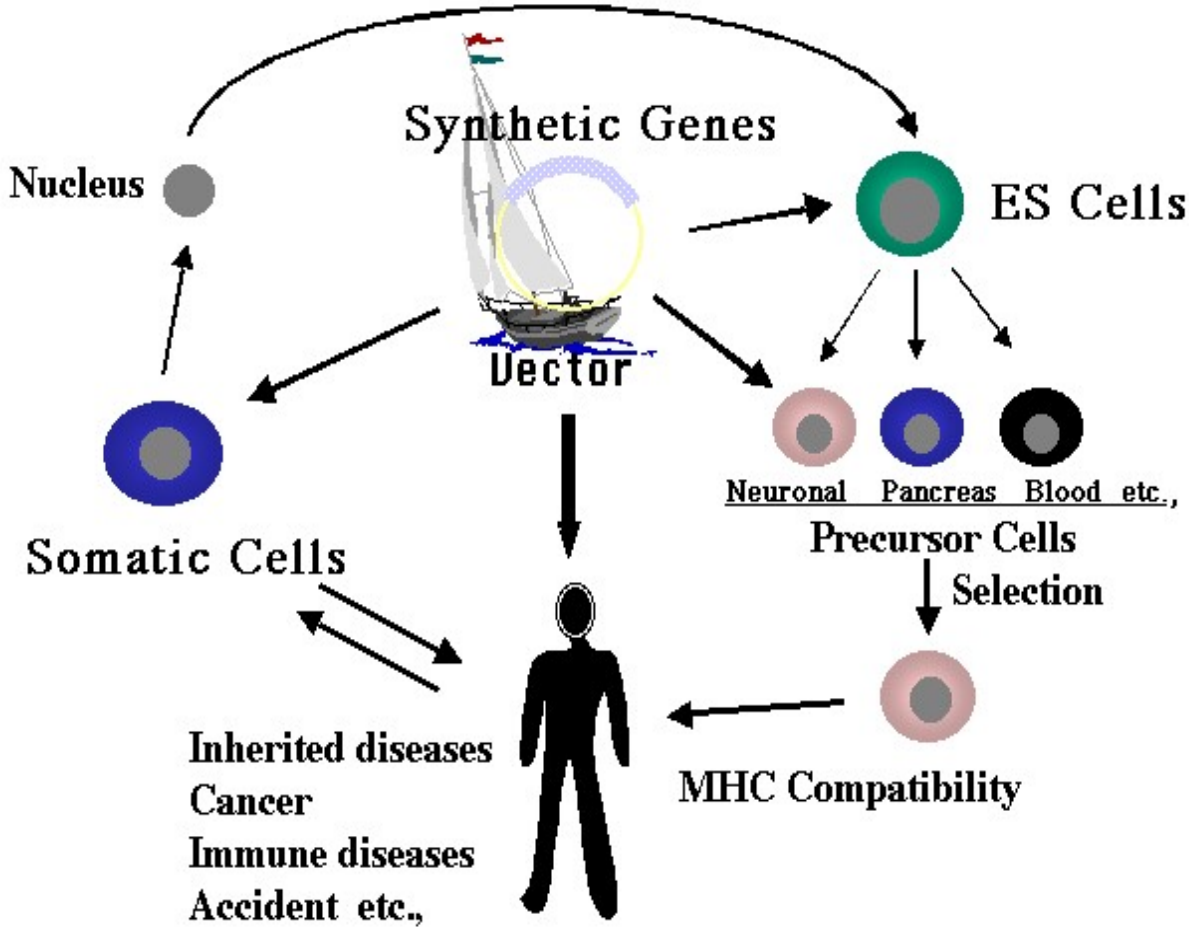


GCSF: endogenous stem cell mobilization treat brain injury



Wu KH, et al. Stem Cell Therapy in Children with Traumatic Brain Injury. Int J Mol Sci. 2023 Sep

GENE/STEM CELL THERAPY

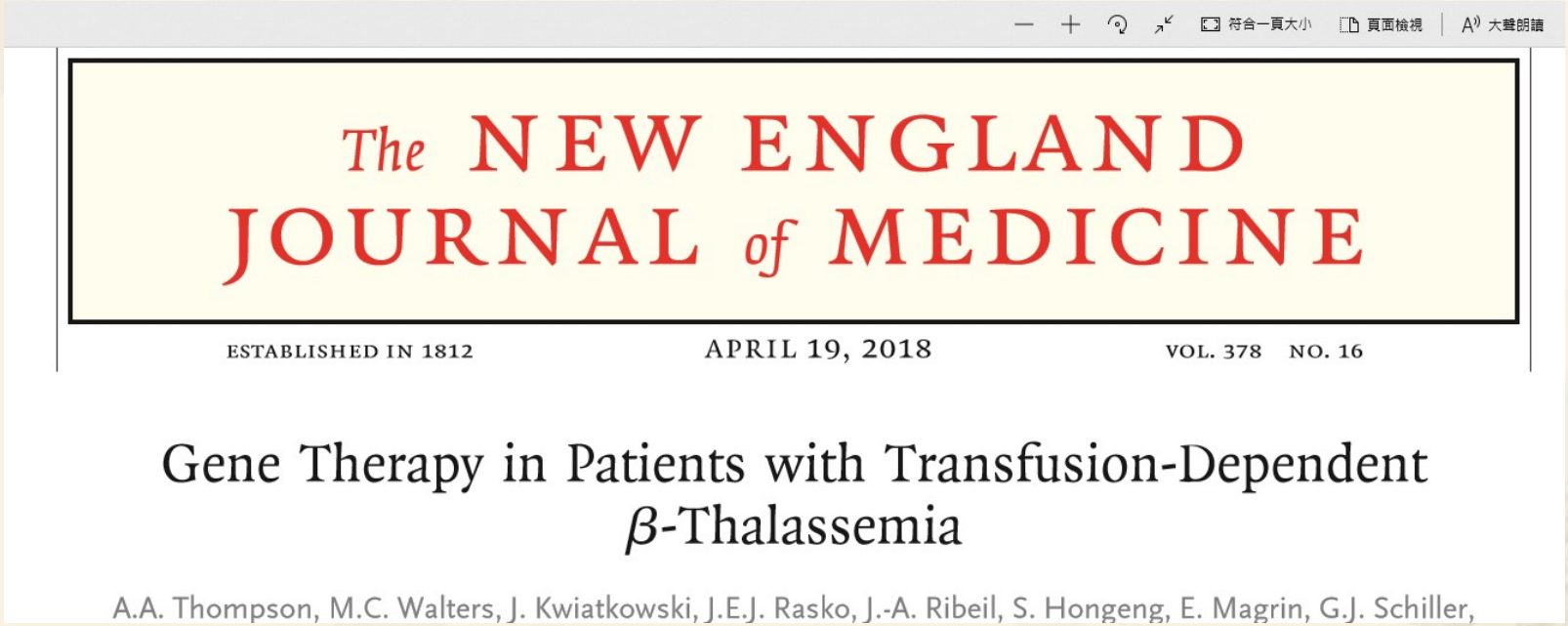


Science. 2009 Nov 6;326(5954):818-23.

Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy.

Nature. 2010; 467: 318-22.

Transfusion independence and HMGA2 activation after gene therapy of human β-thalassaemia.



The NEW ENGLAND JOURNAL of MEDICINE

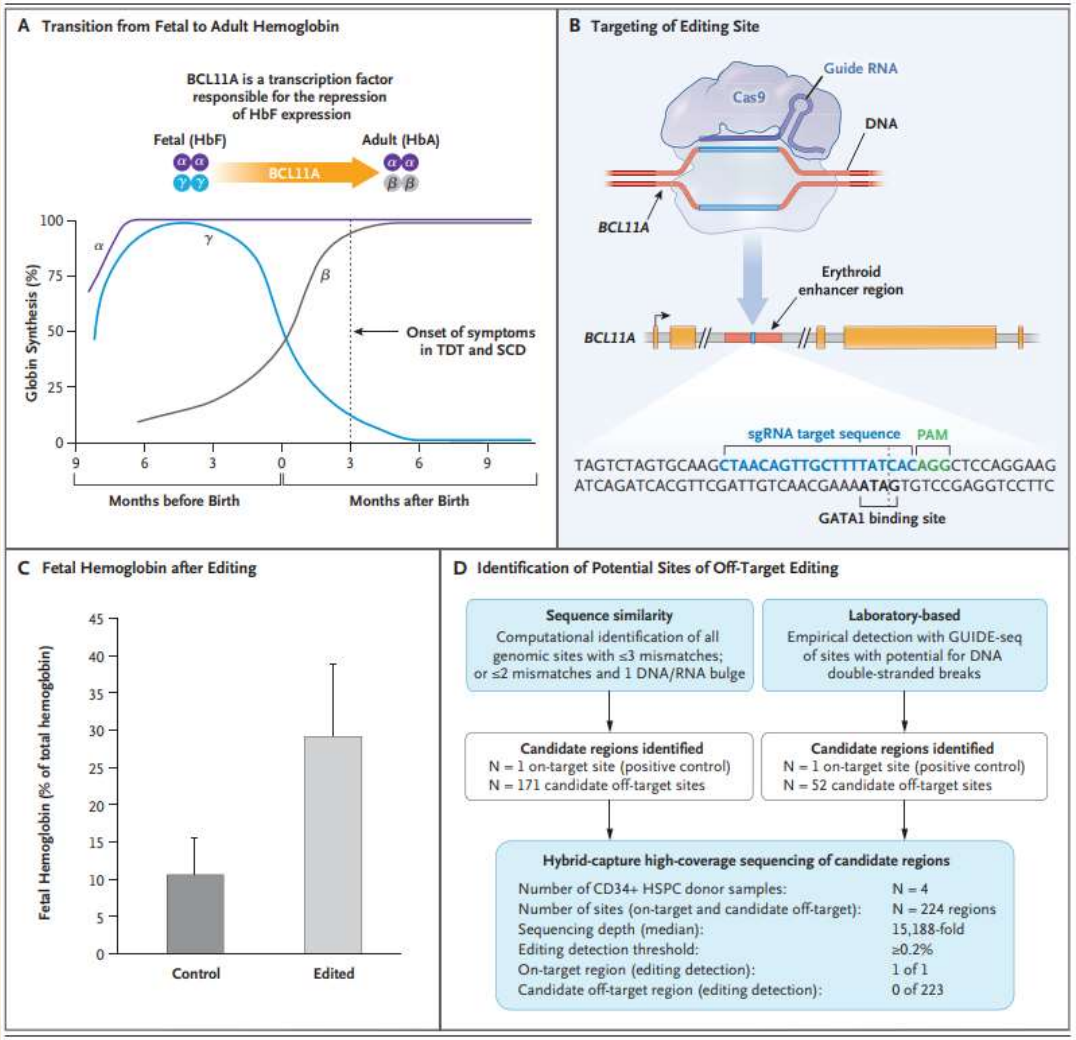
ESTABLISHED IN 1812 APRIL 19, 2018 VOL. 378 NO. 16

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

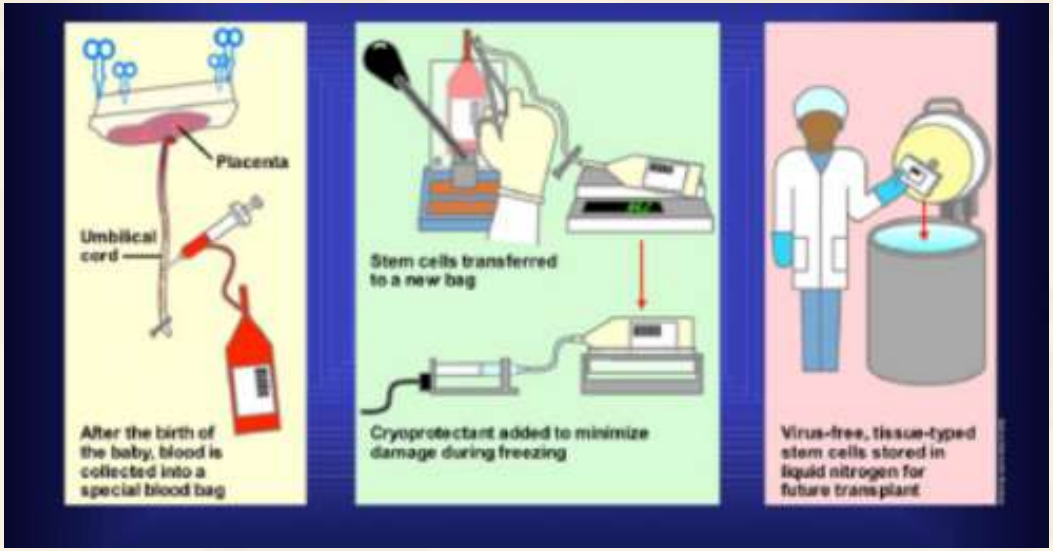
A.A. Thompson, M.C. Walters, J. Kwiatkowski, J.E.J. Rasko, J.-A. Ribeil, S. Hongeng, E. Magrin, G.J. Schiller,

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia.

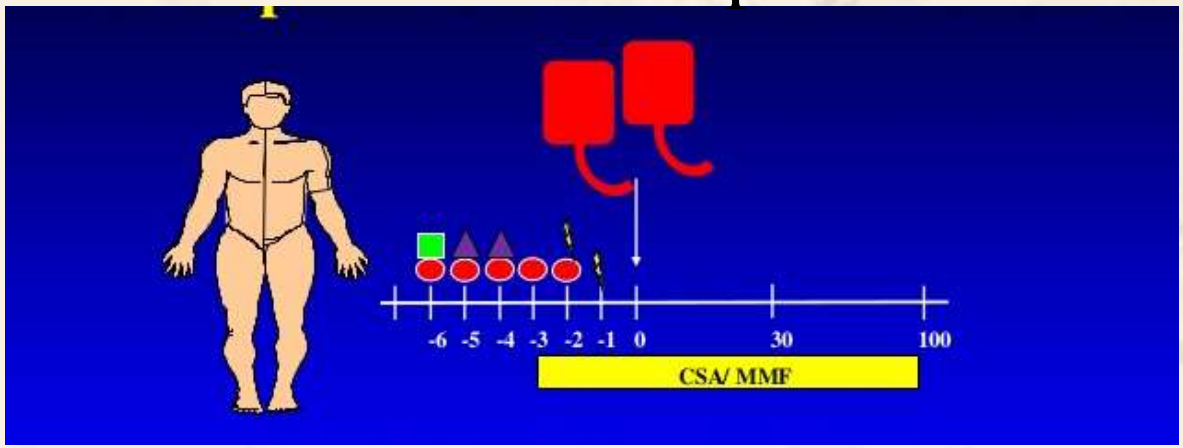
N Engl J Med. 2021 Jan 21;384(3):252-260.



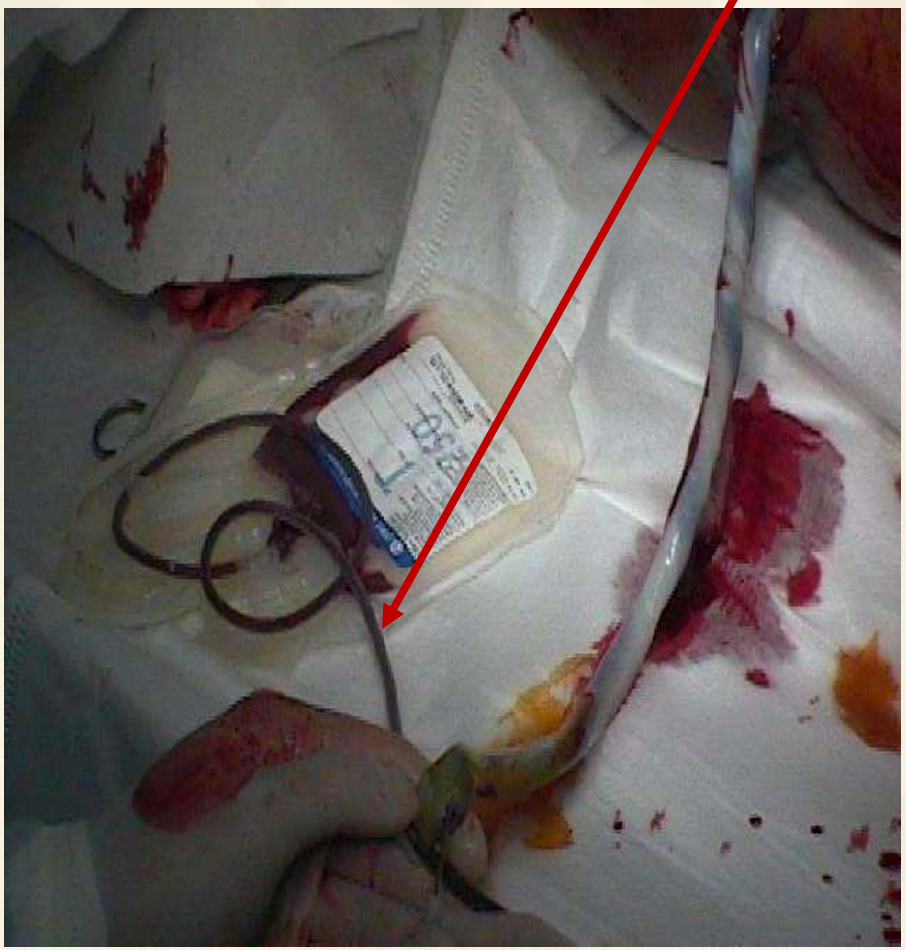
Cord blood collection and banking



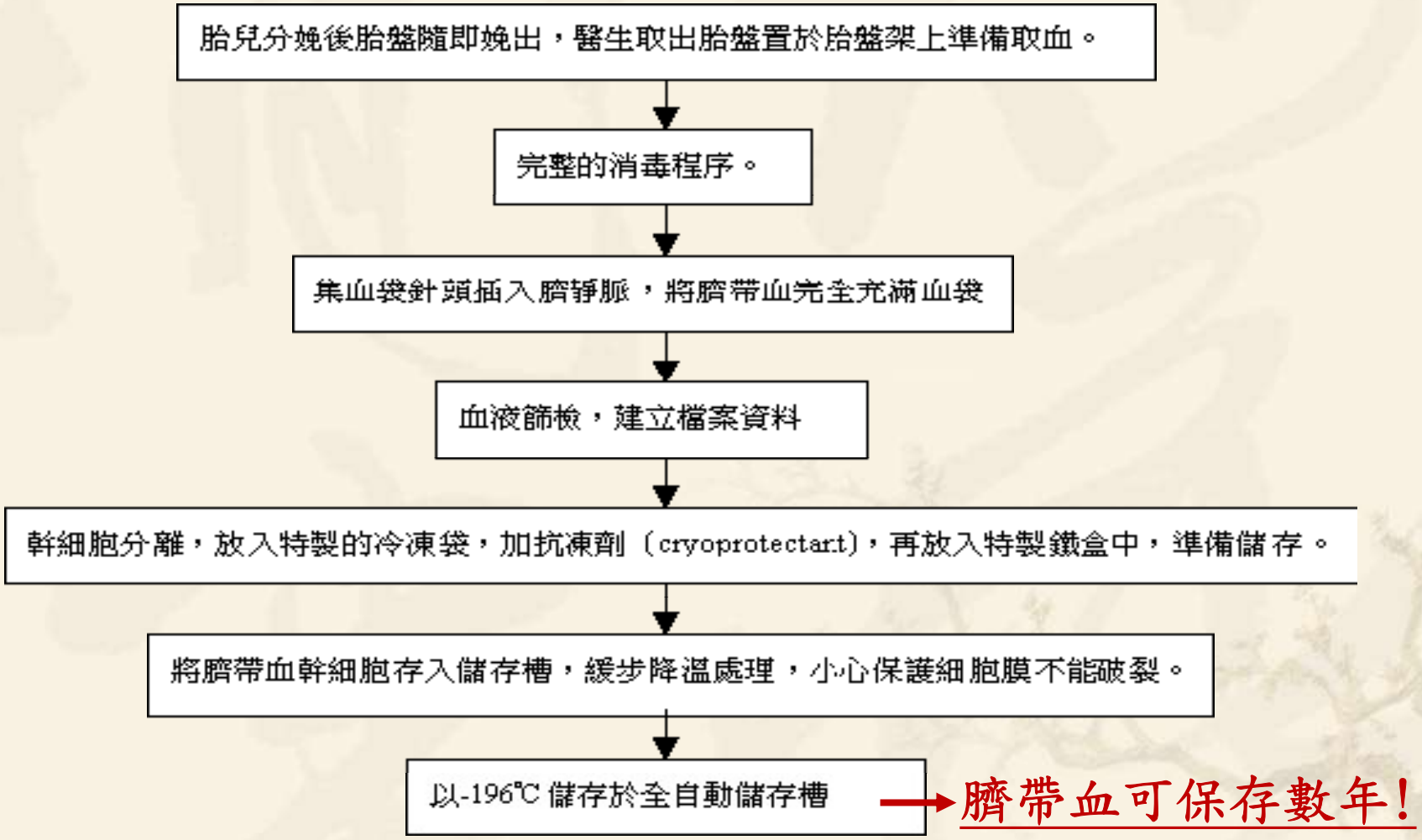
Cord blood transplantation



什麼是臍帶血/臍帶?



臍帶血採集與保存


胎兒分娩後胎盤隨即娩出，醫生取出胎盤置於胎盤架上準備取血。
完整的消毒程序。
集血袋針頭插入臍靜脈，將臍帶血完全充滿血袋
血液篩檢，建立檔案資料
幹細胞分離，放入特製的冷凍袋，加抗凍劑（cryoprotectart），再放入特製鐵盒中，準備儲存。
將臍帶血幹細胞存入儲存槽，緩步降溫處理，小心保護細胞膜不能破裂。
以-196℃儲存於全自動儲存槽
臍帶血可保存數年!

血液的完整檢驗

- 產婦血液進行疾病傳染篩檢: T細胞病毒(Anti-HTLV)、B、C型肝炎(HBsAg、Anti-HCV)、梅毒(RPR)、愛滋病(Anti-HIV)
- 臍帶血細胞進行嚴格檢測及品質控管: ABO、Rh血型，血球細胞計數(分離回收率)、CD34幹細胞計數，幹細胞存活率(Viability)，細菌培養

何謂臍帶血庫

- 公捐 vs 私人 vs 存捐互利：

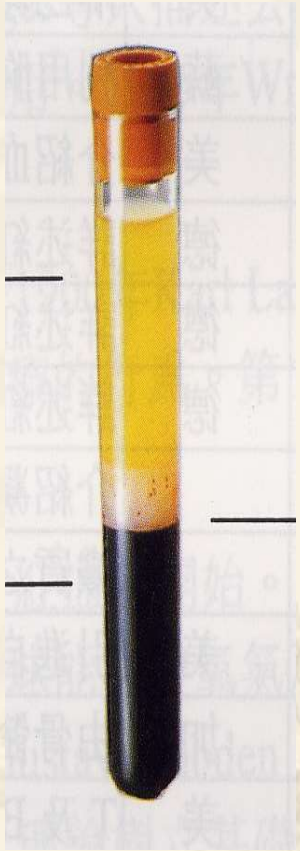
  公捐：就是將臍帶血捐出(捐出後即和此臍帶血無關)，存放在臍帶血庫中，當有病患需要時，和臍帶血庫進行配對，如有合適的臍帶血即將臍帶血取出進行移植

- 目前台灣的公捐臍帶血庫：

  1. 台灣血液基金會
  2. 和信醫院
  3. 慈濟醫院臍帶血庫

臍帶血有什麼?

- Plasma
- Cells: WBCs, RBCs, Platelets
- Nucleated cells (TNCs)
- Hematopoietic stem cells (HSCs)
- Mesenchymal stem cells (MSCs)
- Other progenitor cells



臍帶血的應用

造血幹細胞的移植(以前叫骨髓移植)：

1. 傳統骨髓移植
2. 周邊血液幹細胞移植
3. 臍帶血移植，因此臍帶血移植治療的疾病和骨髓移植 (造血幹細胞的移植)是相同的

臍帶血應用上之優點

1. 不會傷害母體及胎兒，同時沒有骨髓移植麻醉的危險及疼痛、住院等不便。
2. 含有較年輕、豐富的造血幹細胞，造血功能較骨髓強。
3. 臍帶血病毒帶原率較骨髓低，可減少巨細胞病毒感染機率，安全性較高。
4. 臍帶血發生**移植物抗宿主疾病**的機率較低且病情也較輕
5. 臍帶血之免疫寬容性較高，可容許兩個淋巴球抗原位址之差異，仍 可進行移植。同時不須具親屬血緣關係，可以提供更多移植的機會。
6. 少數族群因獨特的遺傳基因，骨髓銀行常無法提供適合的骨髓來源。
7. 臍帶血經收集、冷藏後可以隨時取用，縮短找尋骨髓者的時效（平均縮6個月），不必大費周章協調，不會耽誤病情。

臍帶血移植之問題

1. 臍帶血的造血幹細胞有限，
2. 植入後恢復時間長，感染風險高，隔離住院期間長
3. 血小板恢復慢，易出血。
4. 臍帶血的移植物抗宿主疾病機會少，因此有些報告認為在惡性疾病可能有較高的復發率。
5. 臍帶血是否有先天的基因缺陷，是否會將此基因缺陷移入病患?
6. 臍帶血的品質問題，擁有權問題，倫理問題，法律問題，都是需要考慮的。

臍帶血移植之問題

一單位臍血所含的幹細胞數目不足，對一位成人體重而言，有些人是不夠用的，如何克服:

1. 目前可將二單位或二單位的臍帶血同時植入成人來克服幹細胞數目的不足。
2. 將 臍帶血”增大”(?) 的使用也可克服幹細胞數目的不足。
3. 加入間質幹細胞。
4. 增加Homing to bone marrow 的方法。

Clinical trial of UCB expanded *ex vivo*

Table 1 Summary of clinical trials evaluating UCB that has been expanded *ex vivo*

Type of expansion	*Authors*	*Subjects*	*Cytokines*	*Days in culture*	*Fold expansion*		*Days to ANC >500*	*Days to plts >20000*	*Survival (median length) and GVHD*
					TNC	*CD34⁺*			
Liquid suspension	Shpall *et al.*	$n=37$, adults and children	SCF, TPO, G-CSF	10	56	4	28	106	32% survival (minimum 17 months) 67% grade II–IV aGVHD 40% grade III and IV GVHD
	de Lima and Shpall	$n=35$ adults and children	SCF, TPO, G-CSF	14	23	2.3	14	34	48% survival (11 months) 43% grade II–IV aGVHD 7% grades III and IV
	de Lima and Shpall	$n=10$ adults and children	SCF, FL, IL-6, TPO, TEPA	21	219	6	30	48	30% survival (25 months) 44% grade II aGVHD No grade III and IV aGVHD
	Delaney *et al.*	$n=5$ adults and children	Notch ligand δ-1, SCF, FL, IL-6, TPO, IL-3	16	660	160	14		83% survival (277 days)
Stromal co-culture	de Lima and Shpall	$n=6$ adults and children	SCF, TPO, G-CSF	14	12	12	14.5	30	83% survival (12 months) 33% grade II aGVHD No grade III or IV aGVHD
Continuous perfusion system	Jaroscak *et al.*	$n=27$ children, few adults	PIXY321, FL, EPO	12	2.4	0.5	22	71	39% survival (41 months) 36% grade II–IV aGVHD 22% grade III and IV aGVHD
	Pecora *et al.*	$n=2$ adults	PIXY321, FL, EPO	12	2.2	1.6, second did not expand	28	56	100% survival (13 months) No aGVHD

- Stem Cells. 2006 Nov;24(11):2592-602.
- HOX decoy peptide enhances the ex vivo expansion of human umbilical cord blood CD34+ hematopoietic stem cells/hematopoietic progenitor cells.
- Abstract

HOX transcription factors play important roles in the self-renewal of hematopoietic cells.

decHOX might be a useful new tool for the ex vivo expansion of hematopoietic stem/progenitor cells.

臍帶血/造血幹細胞的現在和未來

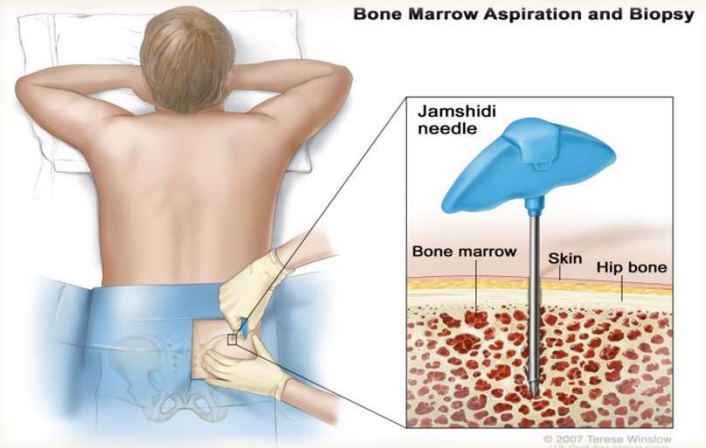
- 目前臍帶血幹細胞用在免疫不全、癌症治療或再生不良性貧血方面，
- 近年來，科學家已成功的將臍帶血幹細胞用來修補受到損傷的各種不同組織，不久的將來，人類很快能夠用自己的臍帶血幹細胞分化發育出新的器官來置換受傷害的器官，
- 未來應該還可以用在基因治療上，用來矯正基因缺失，和治療自體免疫疾病，先天性異常的遺傳疾病病人。

Definition of mesenchymal stem cell

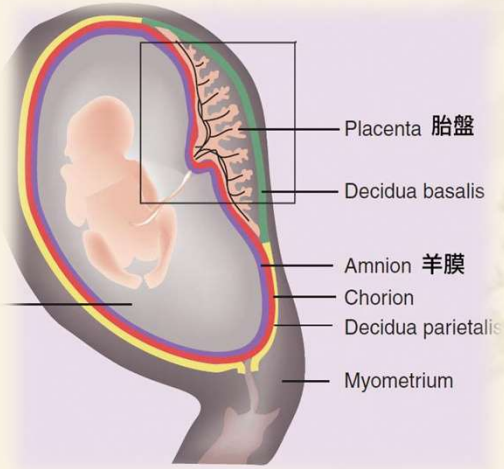
- Capable of diffeentiating into cells and tissues originated from the embryonic mesoderm
- Self-renewal
- Fibroblast-like, plastic adherent
- Surface phenotype: CD29, CD44, CD73, CD105, CD166(+); CD34(-), CD133(-) and Lin-
- Still no operational definition

Where Can We Isolate MSCs?

- Adult-type MCSs:
  - bone marrow
  - Adipose tissue



- **Fetal-type MSCs:**
  - placenta, amniotic fluid, amniotic membrane, umbilical cord



MSC: Appealing characteristics

- Pluripotent-self renewal and wide differentiation into multiple lineages
- Can home to the bone marrow (damaged tissues)
- Can be incorporated direct into other tissues
- Low immunogenicity and suppress alloreactive T cell response (transplanted allogenic MSC are not rejected)

Pleiotropic (多效的)properties of MSCs

1. Anti-inflammatory properties
2. Homing to sites of damage and inflammation
3. Trophic influence on tissue repair
4. Anti-apoptosis, angiogenesis, growth factor production, neuroprotection, anti-fibrosis

Cell Stem Cell. 2015 Jul 2;17(1):11-22.

Clinical applications/trials of MSCs

1. Immune suppressive properties of MSCs (GVHD, Crohn's disease, multiple sclerosis, et al)
2. Myocardial injury
3. Osteoarthritis/degenerative disc disease
4. Pulmonary disease (bronchopulmonary disease, ARDS)
5. Liver disease
6. Diabetes
7. Ischemic stroke/ALS

Cell Stem Cell. 2015 Jul 2;17(1):11-22.

Conclusion: UCMSCs vs BMMSCs

- UCMSCs vs. BMMSCs:
  1. Easier to collect
  2. Less suffering to the donors
  3. Expand faster

  These indicate UCMSCs might be the ideal candidates for cell-based therapy
- The more immunosuppressive effects of UCMSCs than BMMSCs indicate that UCMSCs might be clinically used in immune disorders

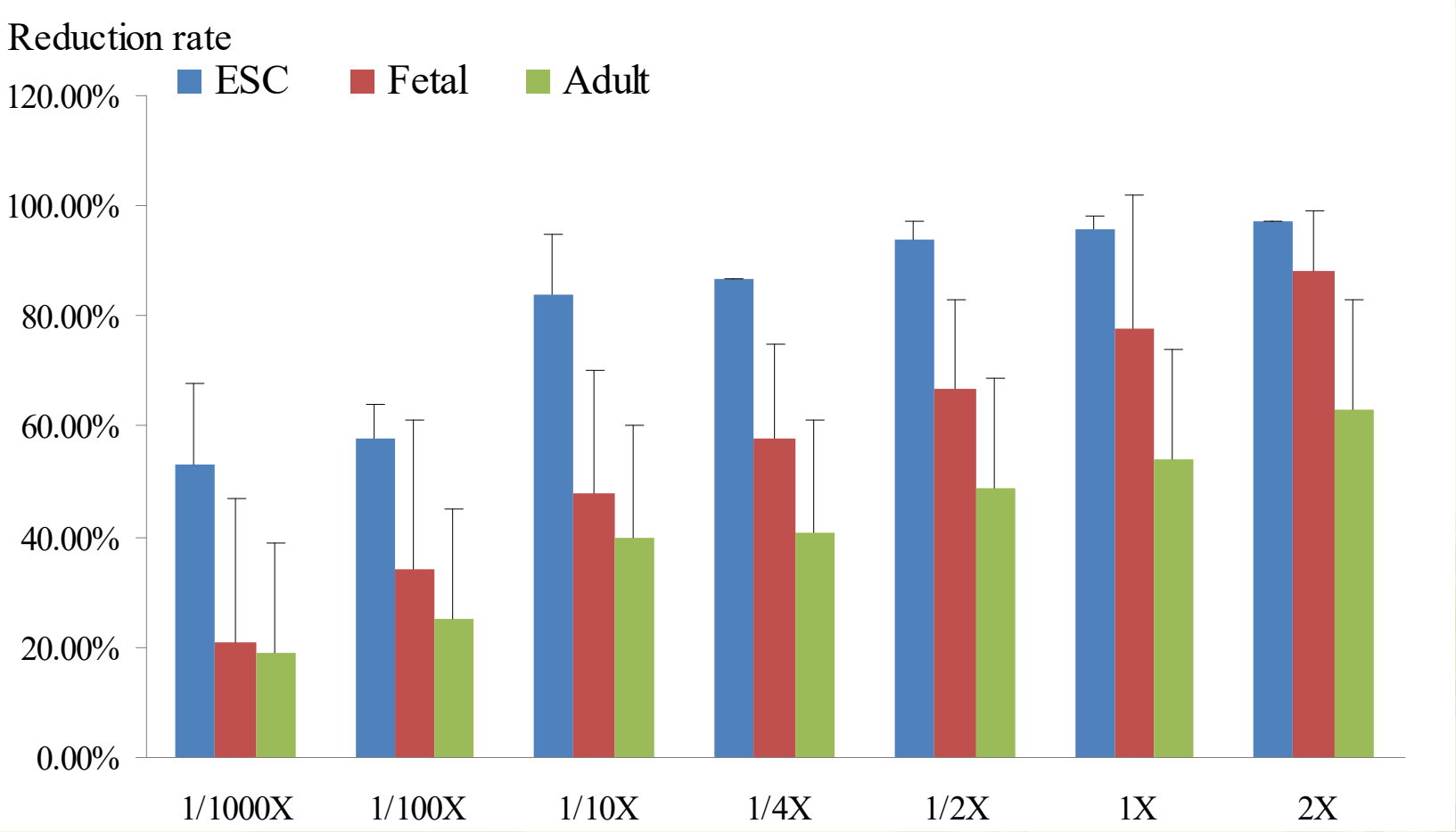
Wu et al, Transplantation. 2011; 91: 1412-6

The Comparison of Interleukin 6–Associated Immunosuppressive Effects of Human ESCs, Fetal-Type MSCs, and Adult-Type MSCs

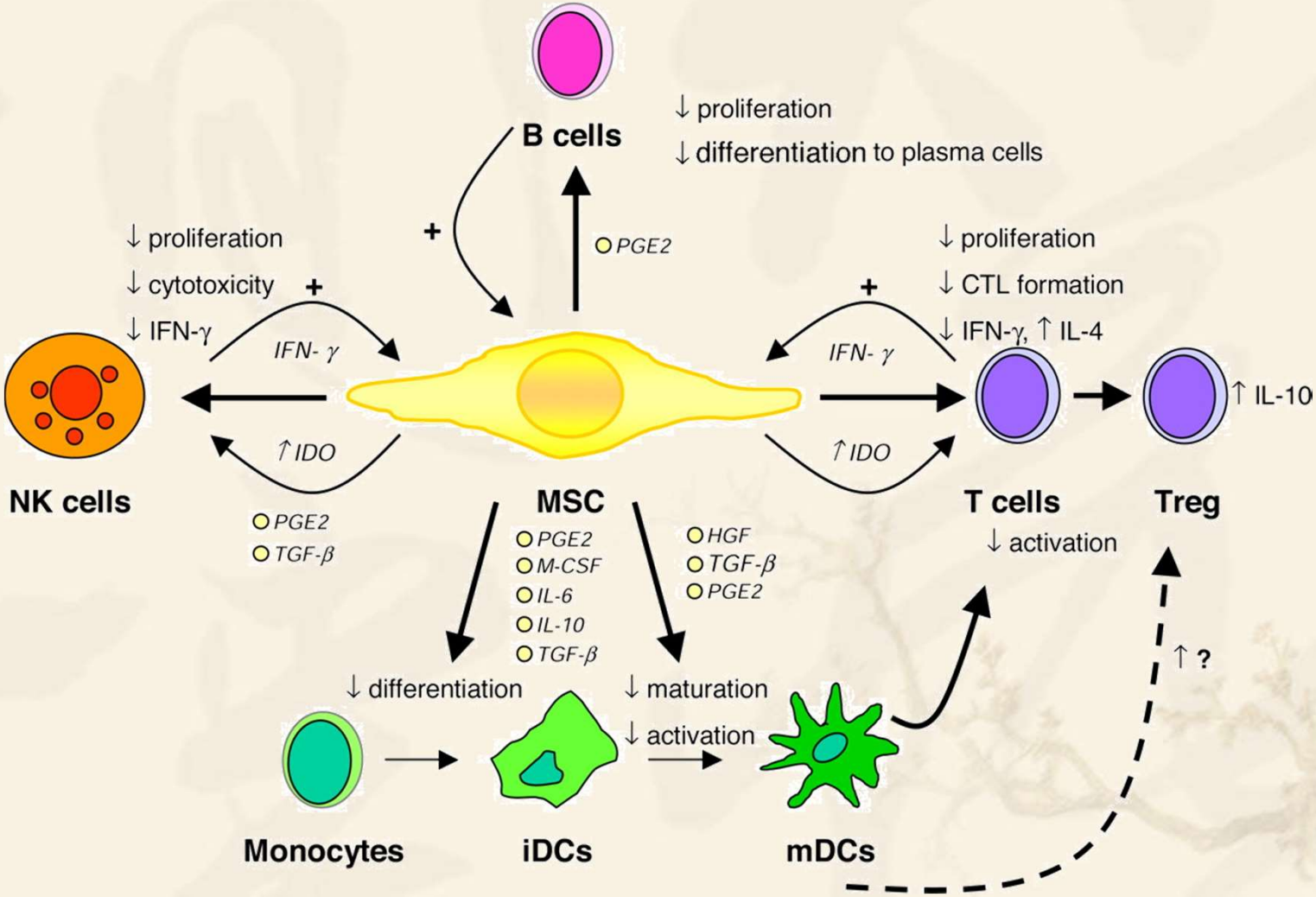
Chin-Kan Chan,[1,2] Kang-Hsi Wu,[3,4] Yun-Shen Lee,[5,6] Shiaw-Min Hwang,[7] Maw-Sheng Lee,[8,9] Shuen-Kuei Liao,[1,10] En-Hui Cheng,[11] Lai-Chu See,[12,13] Chi-Neu Tsai,[1] Ming-Ling Kuo,[14,16] and Jing-Long Huang[15,16]

Wu et al, Transplantation. 2012; 94: 132-8

The Immunosuppressive Effects Comparison Among hESCs, Fetal-Type MSCs and Adult- Type MSCs



Immunomodulatory Effects of MSCs



Immunomodulation of MSC in Animal Study

- **Wu KH**, et al. An increase in CD3+CD4+CD25+ regulatory T cells after administration of umbilical cord-derived mesenchymal stem cells during sepsis. PLoS One. 2014; 9(10):e110338
- **Wu KH**, et al. Time-Series Expression of Toll-Like Receptor 4 Signaling in Septic Mice Treated With Mesenchymal Stem Cells. Shock. 2016
- **Wu KH** et a. The modulation of Th2 immune pathway in the immunosuppressive effect of human umbilical cord mesenchymal stem cells in a murine asthmatic model. Inflamm Res. 2016; 65:795-801.
- **Wu KH** et al. Toll-like receptor signalling associated with immunomodulation of umbilical cord–derived mesenchymal stem cells in mice with systemic lupus erythematosus. Lupus. 2020;29:165-175.

International Journal of
Molecular Sciences

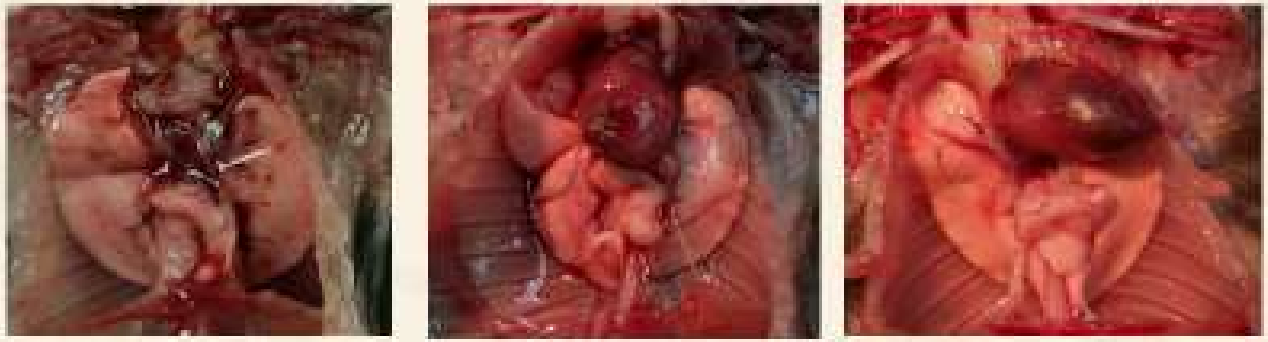
MDPI

Article

Immunomodulation via MyD88-NFκB Signaling Pathway from Human Umbilical Cord-Derived Mesenchymal Stem Cells in Acute Lung Injury

Kang-Hsi Wu [1,2,†], Ju-Pi Li [1,3,†], Wan-Ru Chao [3,4], Yi-Ju Lee [3,4], Shun-Fa Yang [5,6], Ching-Chang Cheng [7] and Yu-Hua Chao [1,2,8,*]

小鼠肺損傷後，以臍帶間質幹細胞治療後，和PBS比較，外觀明顯改善



(a). LPS OA + PBS OA　(b). LPS OA + CMSC OA　(c). LPS OA + CMSC IP

小鼠肺損傷嚴重度。LPS誘發小鼠肺損傷後，(a)以口咽吸入法施加PBS；(b)以口咽吸入法施加臍帶間質幹細胞 (CMSC)；(c)以腹腔注射法施加臍帶間質幹細胞 (CMSC)。

OA: oropharyngeal aspiration
IP: intraperitoneal injection

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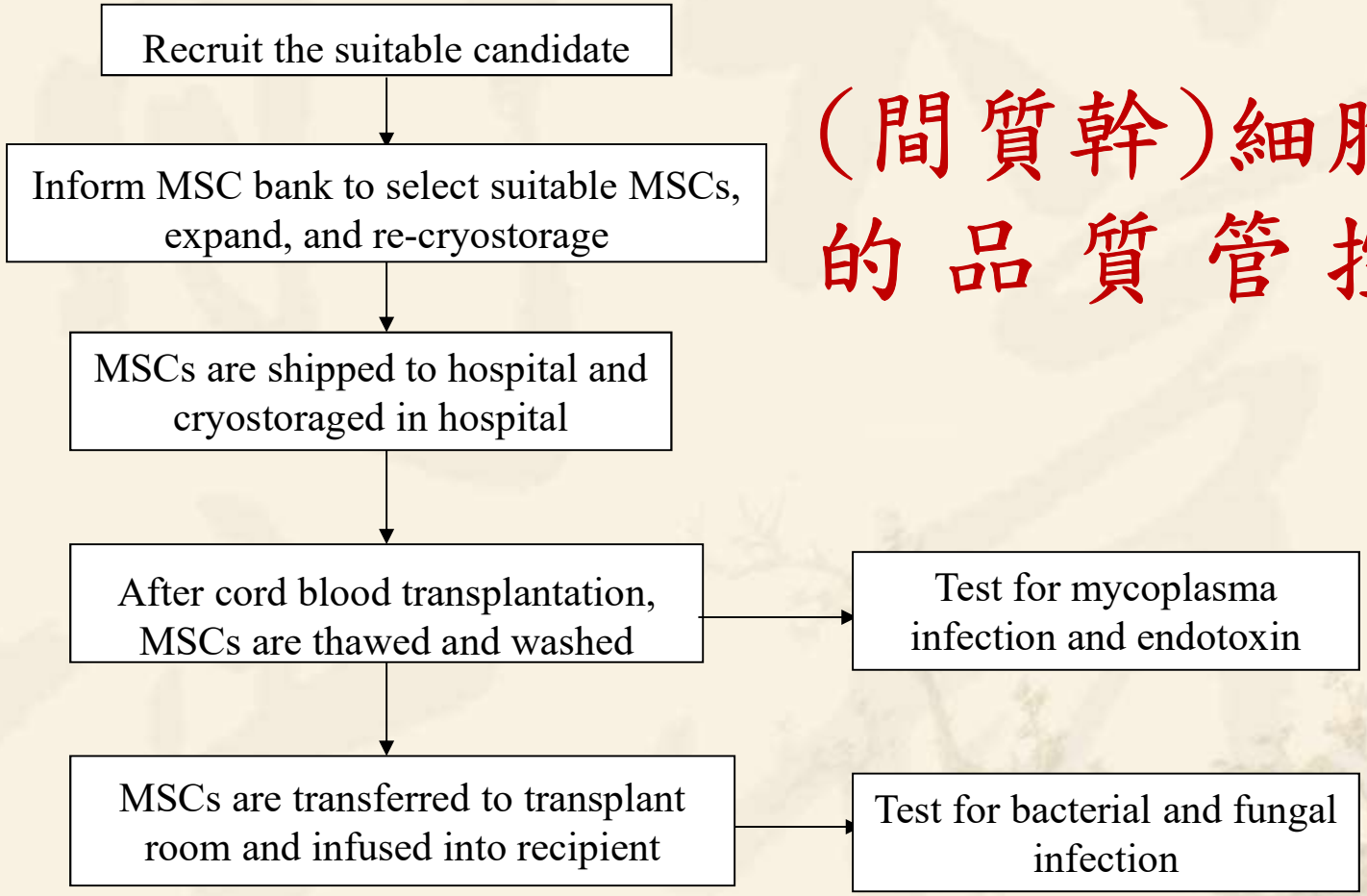
Umbilical Cord-derived Mesenchymal Stem Cells for Severe Bronchpulmonary Dysplasia

Bai-Horng Su, Kang-Hsi Wu, Hsiang-Yu Lin, Ming-Hsia Lin, Ching-Tien Peng, Chris Tsai, (Dr. Su and Dr. Wu are contributed equally to this work) (21 January 2011)

Flow chart for the clinical application of cord MSCs



(間質幹)細胞的品質管控

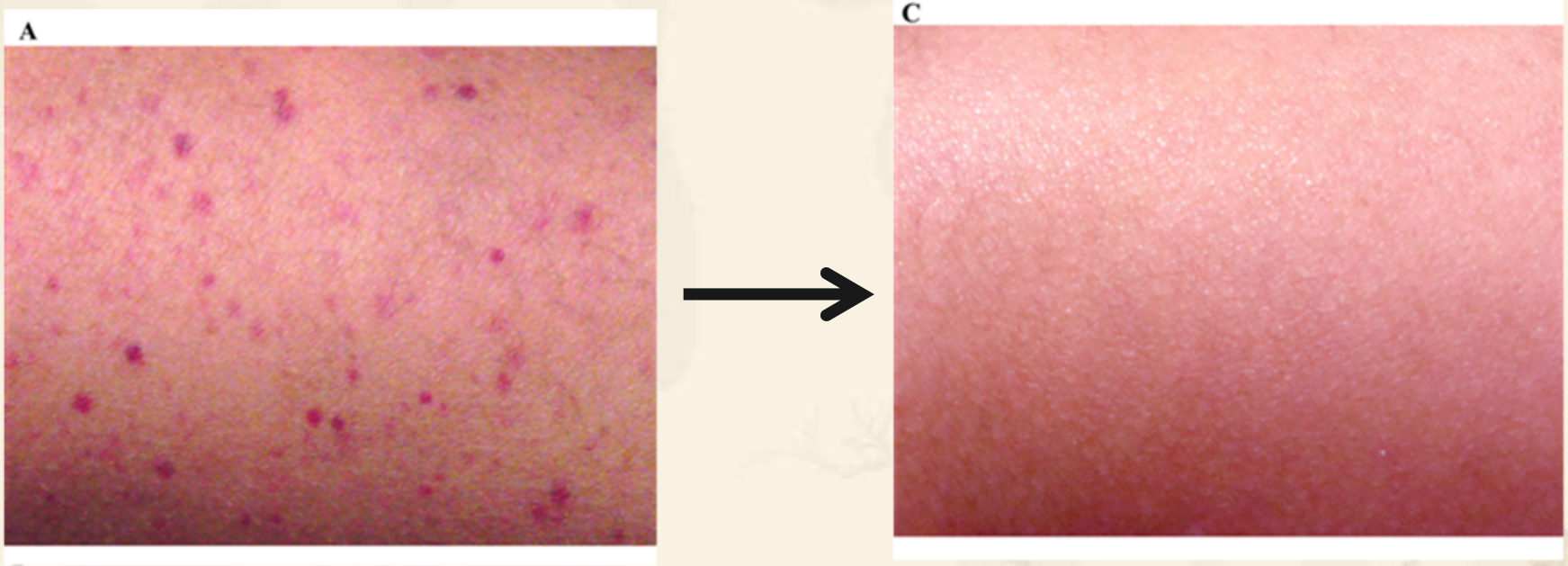
Wu et al, Transplantation, 2013;95(5):773-7

Effective Treatment of Severe Steroid-Resistant Acute Graft-Versus-Host Disease With Umbilical Cord-Derived Mesenchymal Stem Cells

UCMSC are easier to obtain than BMMSC and cause no suffering to the donor, indicating that they might be the ideal candidates for cell-based therapy. The umbilical cord may be an alternative MSC source, similar to UCB as a good source of hematopoietic stem cells. This is the first reported use of UCMSC in a human clinical application, and this procedure seems both feasible and safe. UCMSC were effective against aGVHD in our patients, but prospective, controlled studies with UCMSC are warranted.

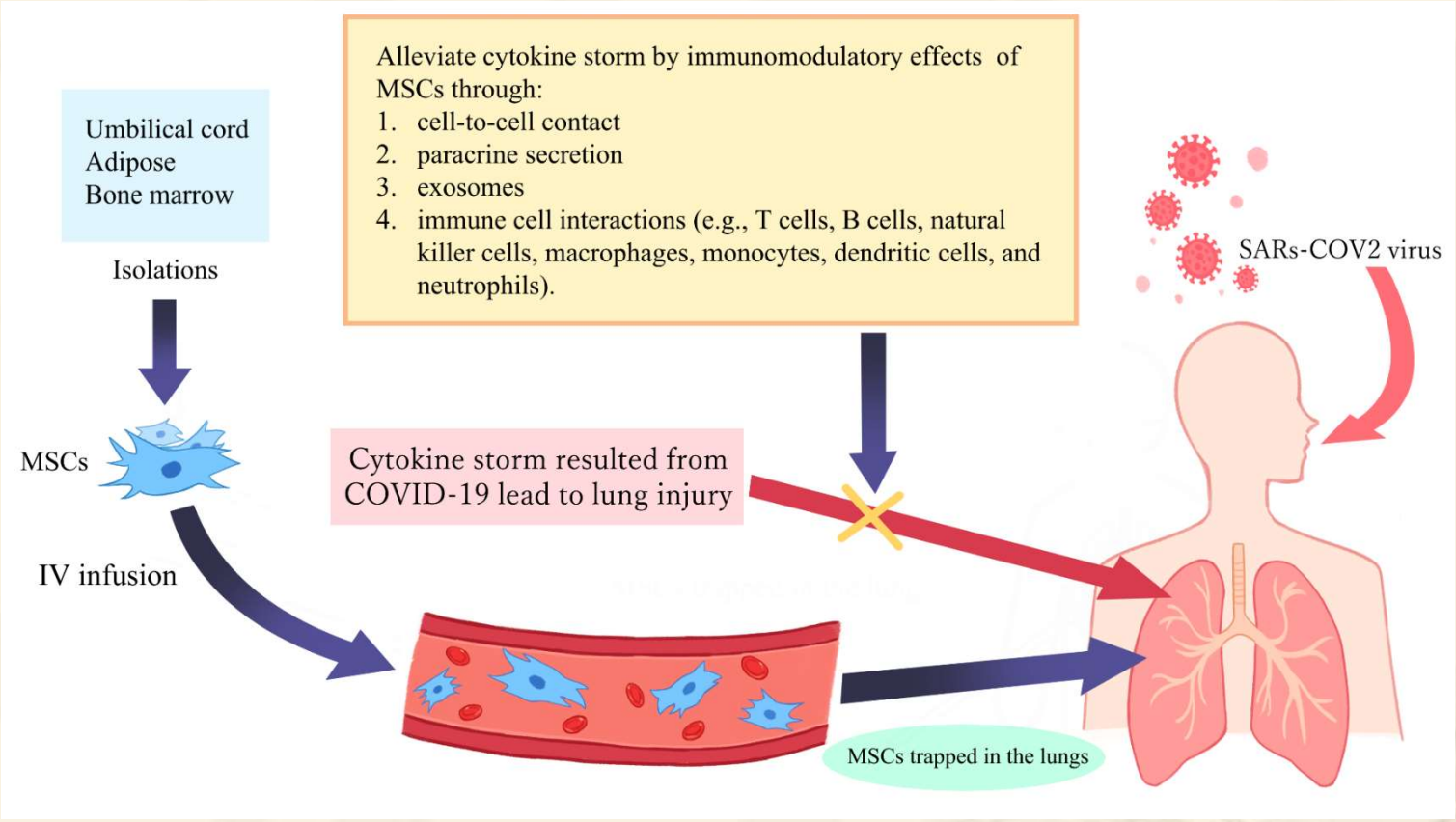
Wu et al, Transplantation. 2011; 91: 1412-6.

GvHD Improved After UCMSC Infusion



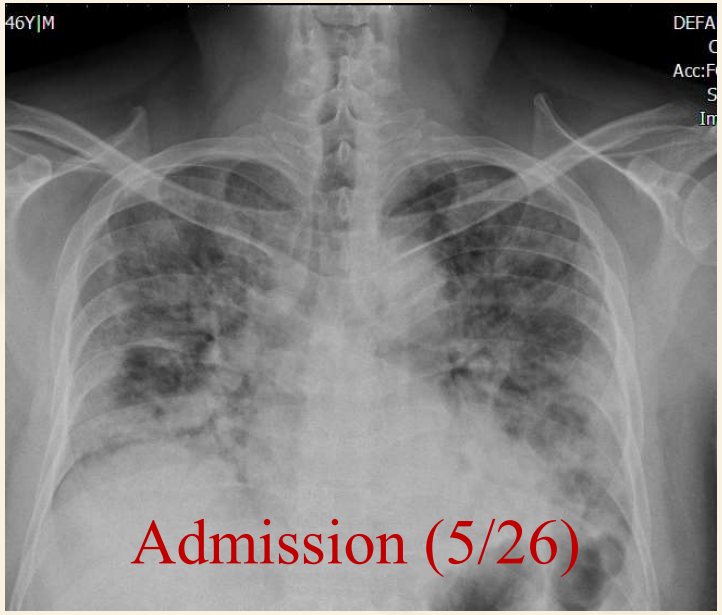
Before UCMSC **After UCMSC**

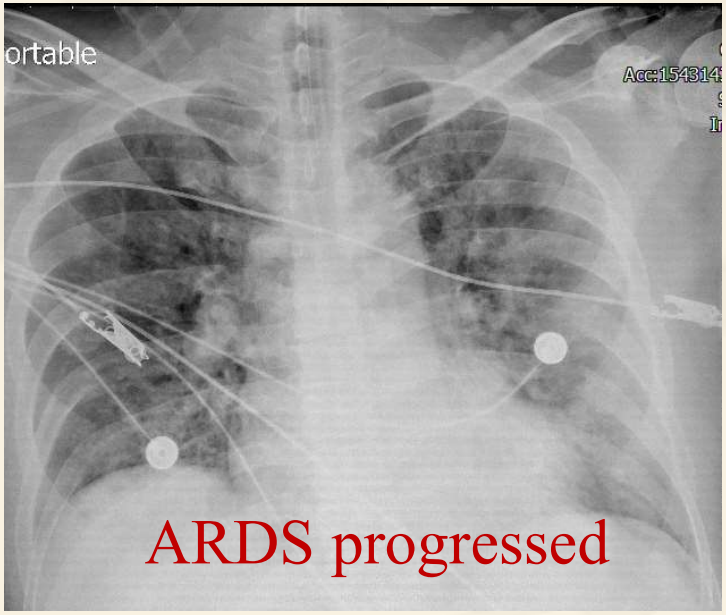
Clinical applications and mechanisms of MSC in treatment of COVID-19

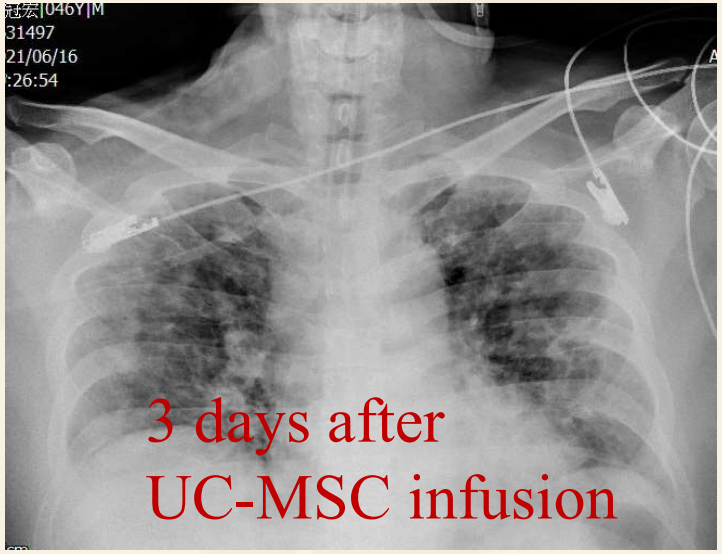


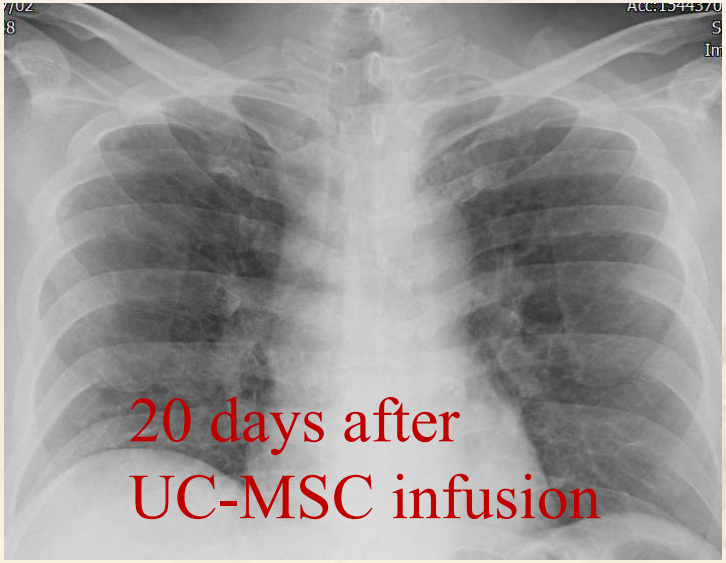
Wu KH et al. Current Pharmaceutical Design 2022

Wu KH, et al. Int J Mol Sci. 2023 Sep

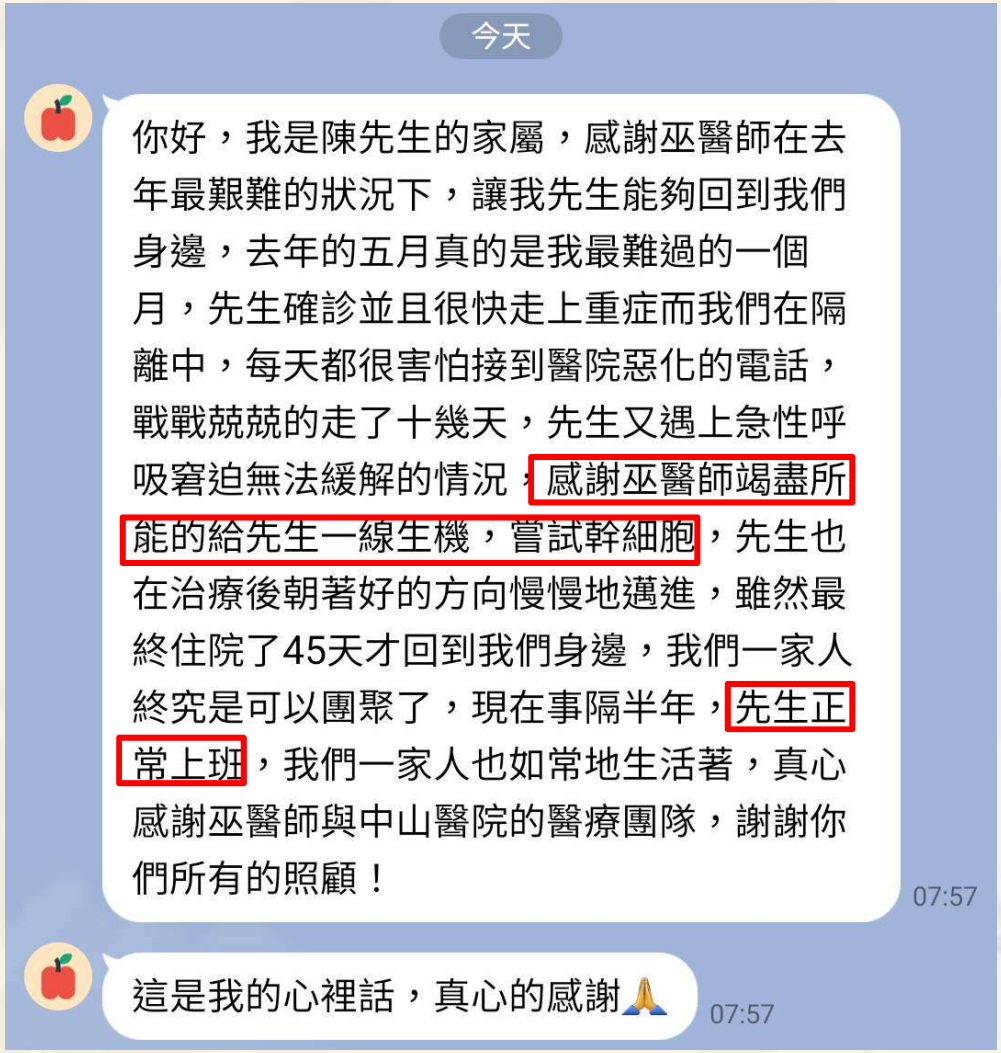

Admission (5/26)


ARDS progressed


3 days after
UC-MSC infusion


20 days after
UC-MSC infusion

醫病人員最大的欣慰



2022/04/18

癌症免疫治療三大分類

三種癌症免疫療法中，藥物療法是最早引進台灣[3]，也是目前最普遍使用的療法。

藥物療法[4]：關掉T細胞煞車

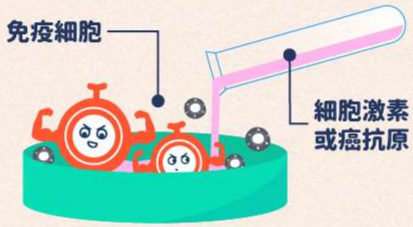
第1種 阻止樹突細胞抑制 T 細胞

第2種 阻止癌細胞抑制 T 細胞

2019 年有 3 種癌症免疫治療藥物已納入健保給付[7]

細胞療法[5]：培養癌細胞殺手

第1種 把免疫細胞抽出來，大量增殖並強化，注射回體內。



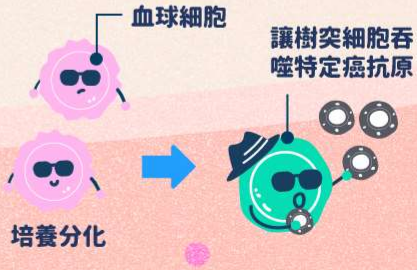
第2種 取出 T 細胞，基因改造成針對性特殊作戰部隊「CAR-T細胞」後注射回體內。

2018 年 9 月「特管辦法」修法開放台灣引進第一種[8]

疫苗療法[6]：癌症治療疫苗

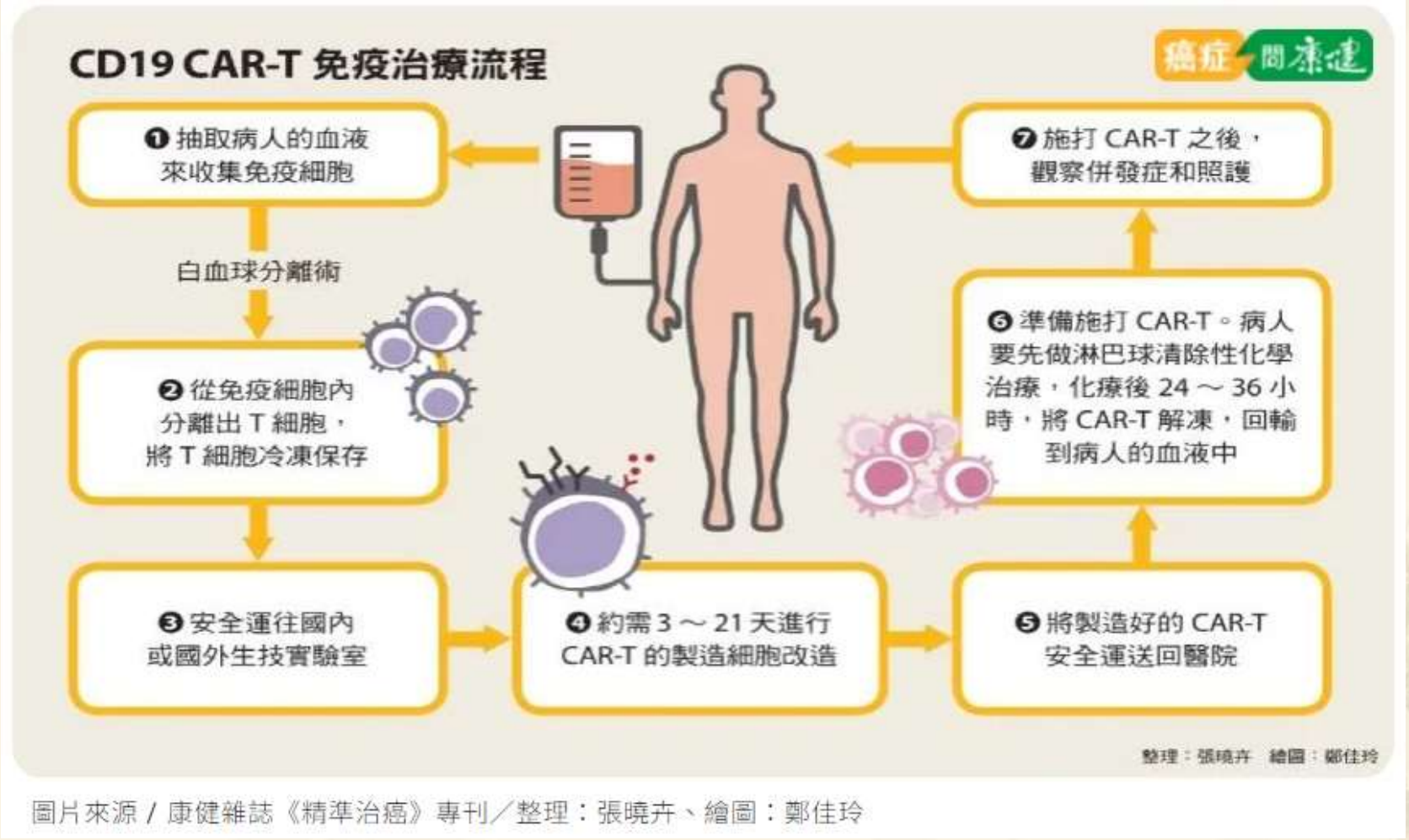
第1種 把癌細胞抗原打入人體激發免疫反應

第2種 將血球細胞培養分化成樹突細胞，注回人體，驅動 T 細胞



國際間仍在研究、臨床試驗階段，廣泛實際應用仍需要時間。

CAR-T治療流程



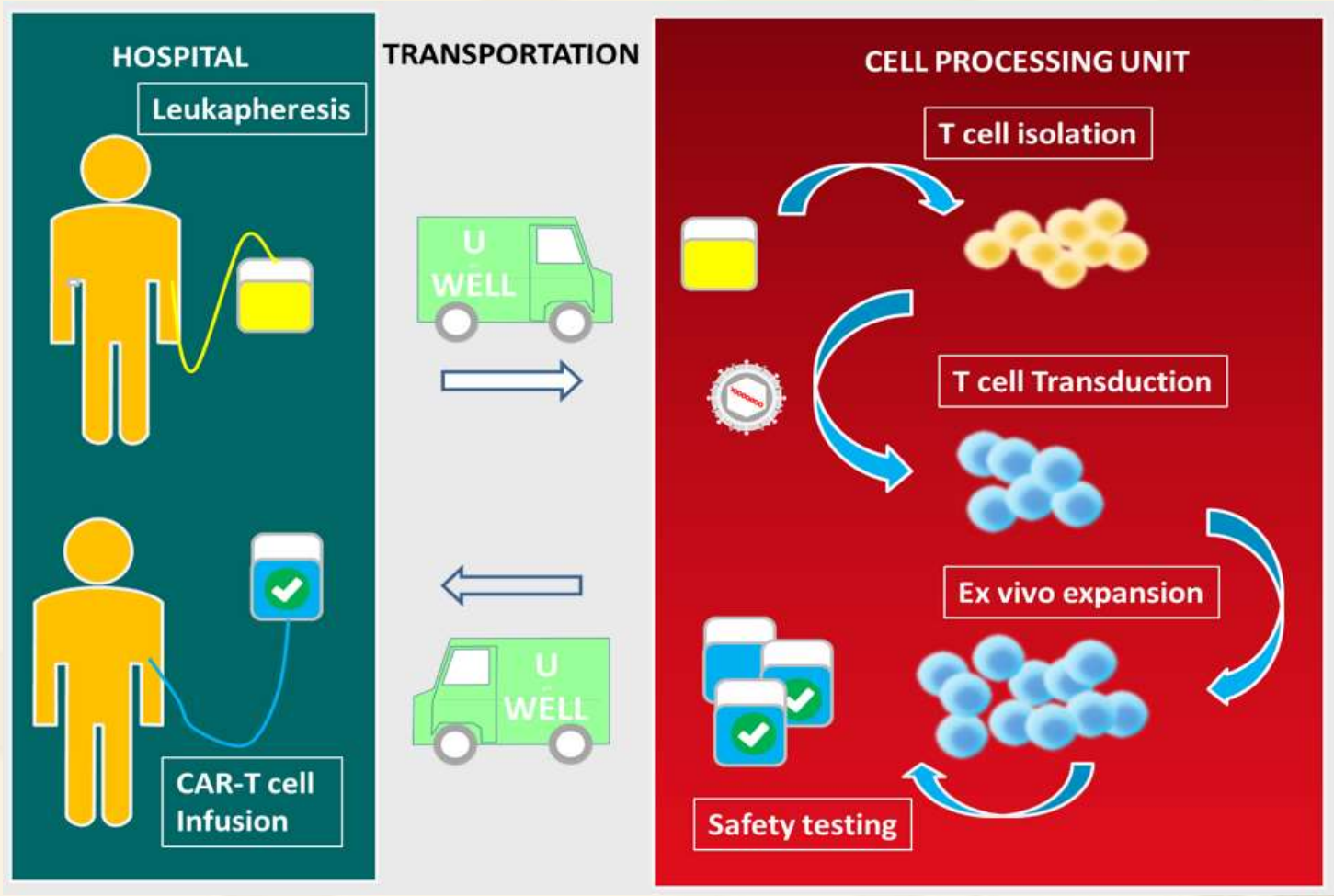
圖片來源 / 康健雜誌《精準治癌》專刊／整理：張曉卉、繪圖：鄭佳玲

Chimeric Antigen Receptor (CAR) T-Cell Therapy

- 2012 年美國女孩 Emily，罹患急性淋巴性白血病，成為全球第一個接受 CD19 CAR-T 細胞治療的兒童。目前在她身體內的癌細胞已經完全根除。
- CAR-T目前臨床主要應用血液癌症的治療: 如血癌，淋巴癌
- 台灣的CAR-T細胞主要來自:
  - Norvatis (台灣TFDA approved)
  - 宇越生技(台灣): 已完成多例恩慈治療，安全有效，
    目前和三總進行成人淋巴癌的臨床試驗中，
    中山附醫於2023/10/18完成CAR-T治療兒童惡性淋巴癌
    中山附醫合作治療兒童急性淋巴性白血病

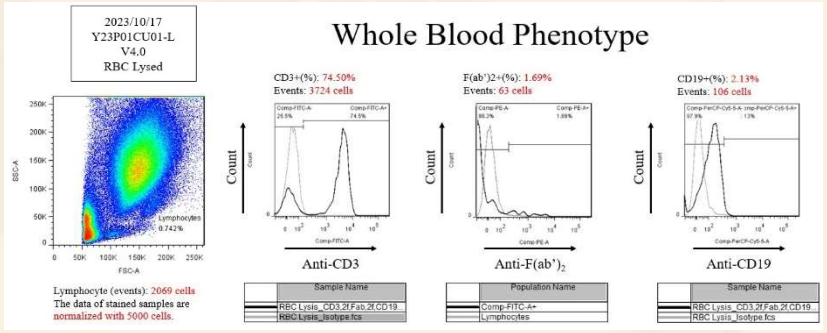

三總攜手突破 CAR-T 啟動
CAR-T Chimeric Antigen Receptor-T
細胞治療淋巴瘤臨床試驗合作案

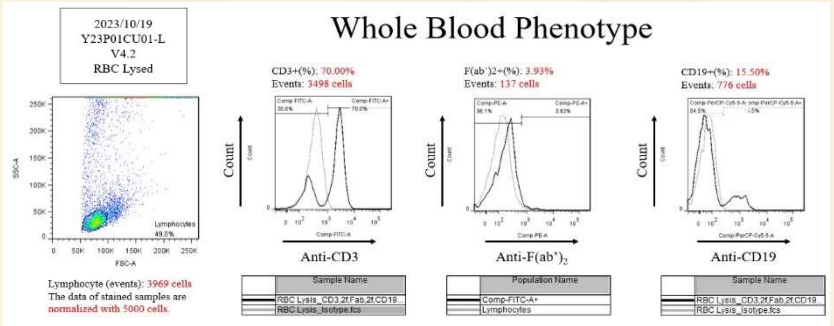
CAR-T 細胞運送和製造生產

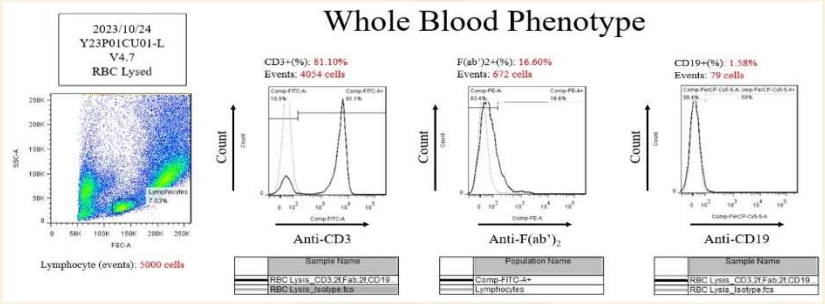


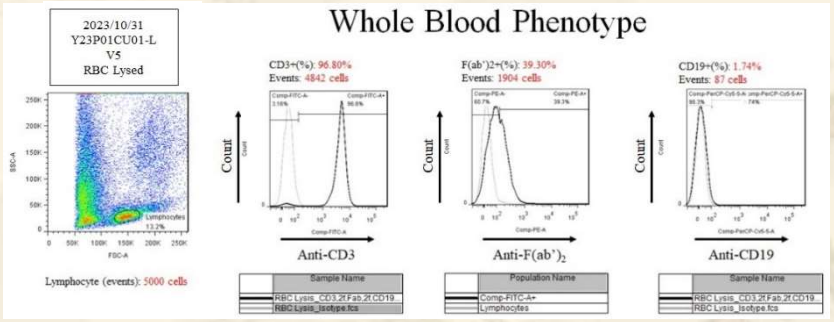
圖來自宇越生醫

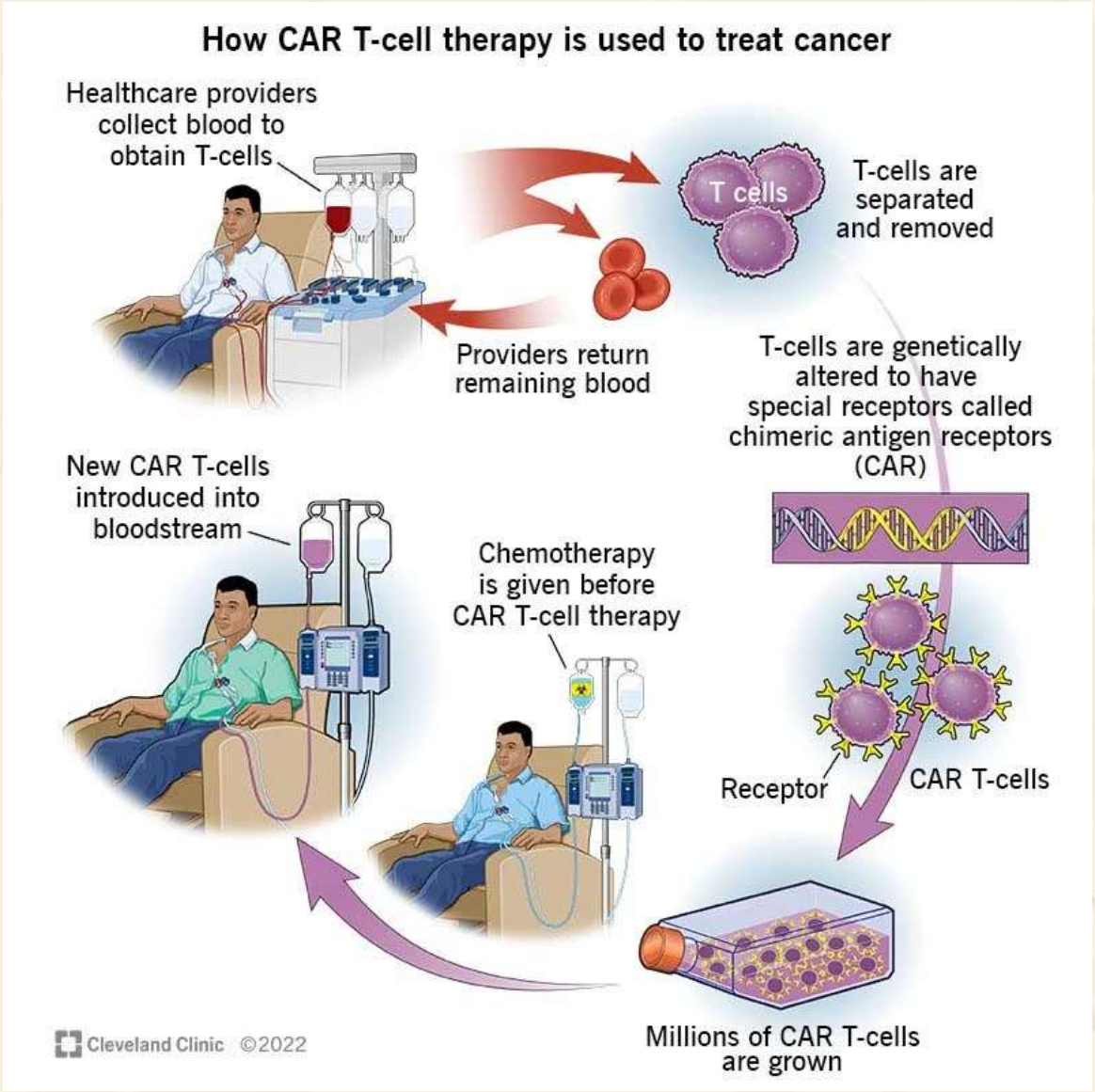
CAR-T cell expansion and B lymphocyte aplasia










How CAR T-cell therapy is used to treat cancer
Healthcare providers collect blood to obtain T-cells
T cells
T-cells are separated and removed
Providers return remaining blood
T-cells are genetically altered to have special receptors called chimeric antigen receptors (CAR)
New CAR T-cells introduced into bloodstream
Chemotherapy is given before CAR T-cell therapy
Receptor
CAR T-cells
Millions of CAR T-cells are grown
Cleveland Clinic ©2022

Multidisciplinary team for CAR-T therapy

細胞治療
實驗室

專科醫師

檢驗科

護理師

社工師

藥師

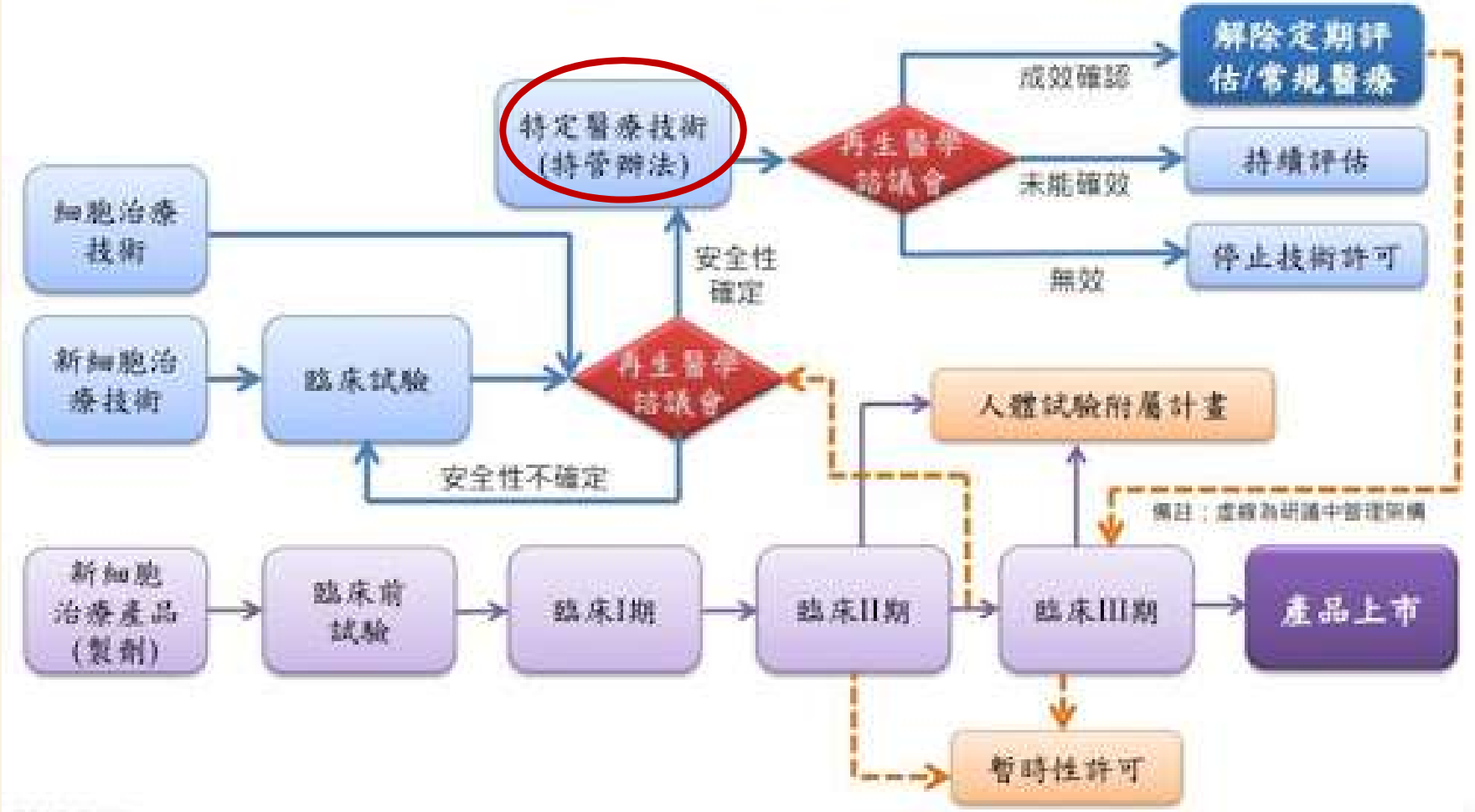
血腫科醫師

ICU

台灣細胞治療的法規

台中中山附醫(幹)細胞治療計畫

細胞治療管理架構


特定醫療技術
(特管辦法)
再生醫學諮議會
成效確認
解除定期評估/常規醫療
持續評估
未能確效
停止技術許可
無效
安全性確定
細胞治療技術
新細胞治療技術
臨床試驗
再生醫學諮議會
人體試驗附屬計畫
安全性不確定
備註：虛線為研議中管理架構
新細胞治療產品(製劑)
臨床前試驗
臨床I期
臨床II期
臨床III期
產品上市
暫時性許可

目前中山附醫(幹)細胞治療計畫(一)

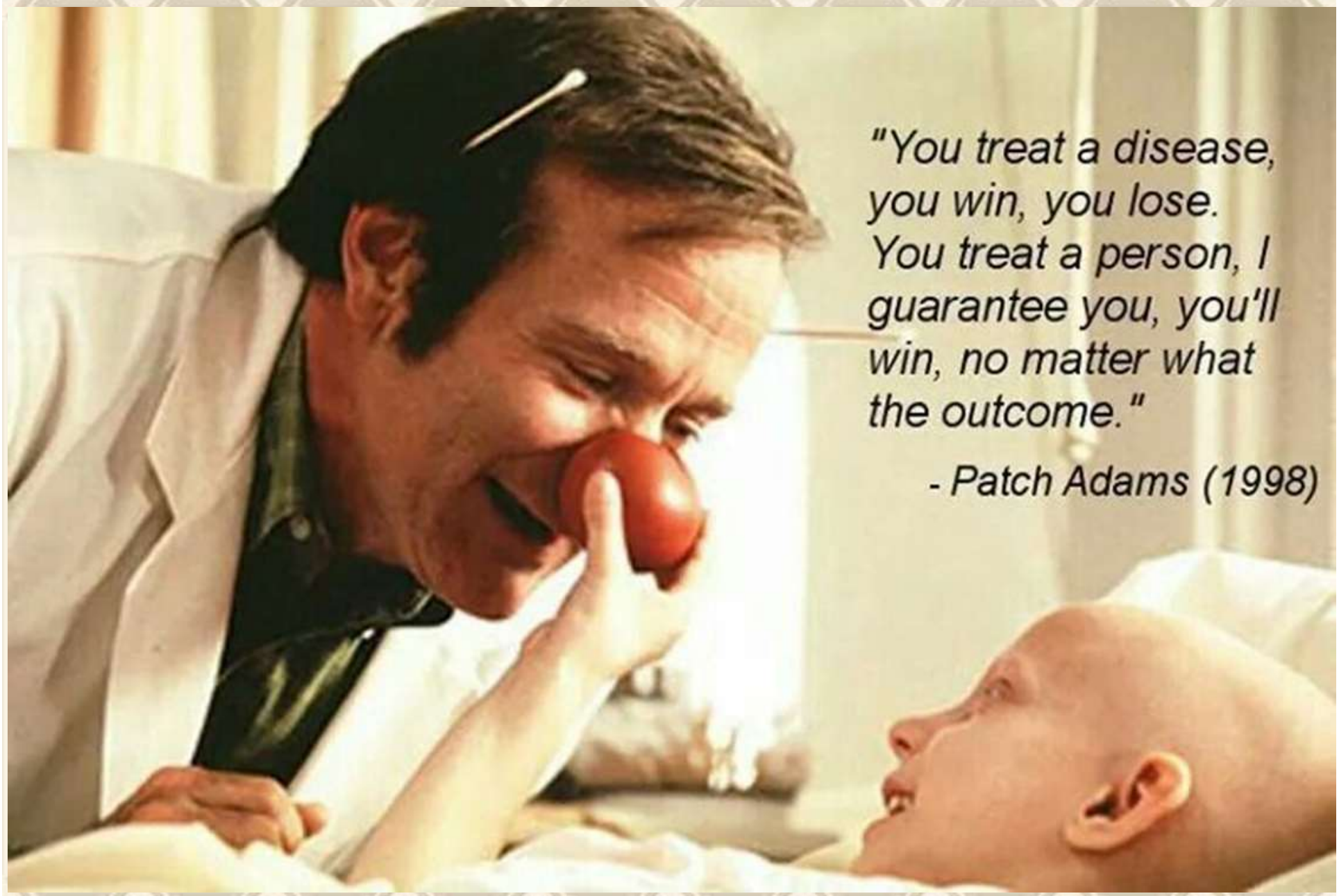
1. 癌症免疫細胞治療: 曹昌堯醫師 (特管法)
2. 幹細胞治療心臟疾病: 翁國昌醫師
3. 自體脂肪間質幹細胞治療困難傷口: 陳俊嘉醫師 (特管法)
4. 自體脂肪間質幹細胞治療退化性關節炎: (特管法)
5. 間質幹細胞治療肺纖維化: (已完成動物preclinical study)，預計申請Phase II 臨床研究，恩慈治療

目前中山附醫(幹)細胞治療計畫(二)

6. 完成臍帶間質幹細胞治療新冠重症 (恩慈)
7. CAR-T治療復發/難治B細胞急性淋巴性白血病(恩慈/IRB請中)
8. D34+ selection周邊血幹細胞治療慢性缺血性腦中風 (特管法)
   (周邊血液CD34+幹細胞分選製程技術建成，收案中)
9. GCSF: endogenous stem cell mobilization treat brain injury
10. CD 34+ 細胞治療嚴重下肢缺血症 (預計申請IRB)

Take Home Message for Cell Therapy

1. 細胞臨床治療時需考量的事項: 細胞品質! 什麼細胞? 治療什麼疾? 治療時機?
2. 造血幹細胞移植(HSCT):
   半吻合造血幹細胞移植: 克服配對的問題
   造血幹細胞治療血液病以外的疾病: 中風和下肢缺血
3. 間質幹細胞(MSC): 異體使用是安全的，在某些疾病確實是有效果的!
4. CAR-T治療: 癌症客制化治療的希望
5. 台灣細胞治療的法規: 好的法規能造福病患，提高台灣的生技業，創造多贏!


"You treat a disease, you win, you lose. You treat a person, I guarantee you, you'll win, no matter what the outcome."
- Patch Adams (1998)

醫人醫病要醫心
最先進的治療，最人性的照護

- 謝謝老師、醫院、長官、同仁、伙伴、好友、同好，謝天以助人
- 給病患多一個選擇，以幫助病人

Thank you for your attention，請大家多指教!

我會將今天大部份的slides放在我網頁上:

上google，key上巫康熙，就可找到|「巫康熙醫師|血液病暨兒童癌症專業團隊」，在這網頁的「特色簡介」中的「最新消息」，就可找到今天演講的slides

如何找到我: 如上，我的網頁，可找到我的聯絡方式

歡迎上我的FB「巫康熙醫師」，大家互相討論和學習