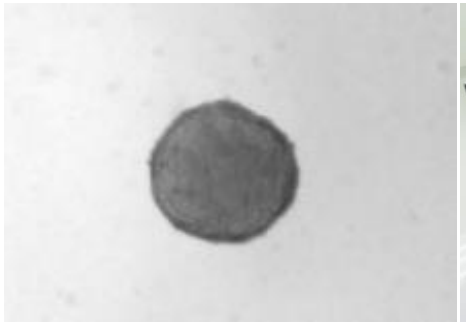
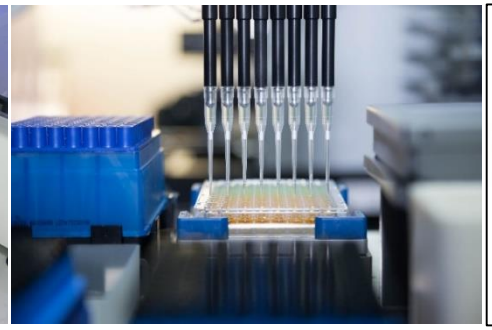
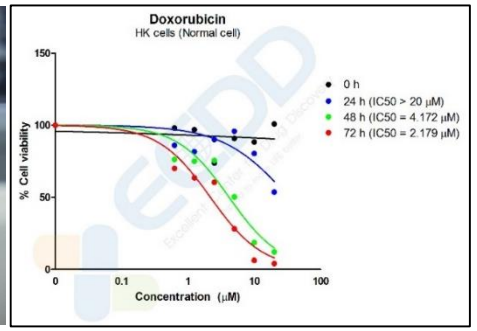
Mahidol University

Wisdom of the Land



Immunotherapy: Innovation Platform for Cancer Treatment

Prof. Suradej Hongeng, M.D.

Division of Hematology/Oncology, Department of Pediatrics
Ramathibodi Hospital, Mahidol University

Dr. Suparerk Borwornpinyo

Excellent Center for Drug Discovery, Mahidol University
Department of Biotechnology, Faculty of Science, Mahidol University

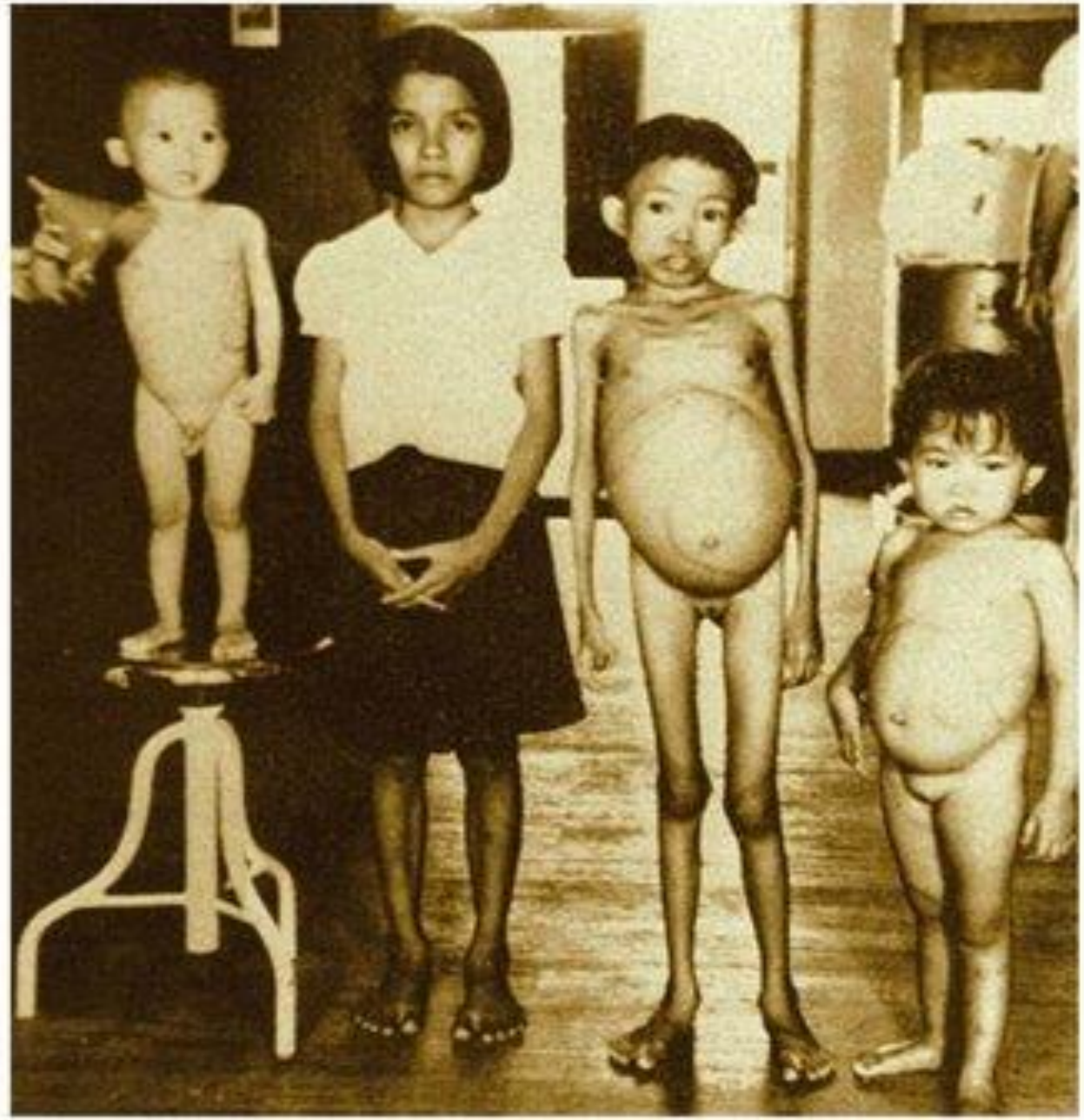
28th March 2019

Gene therapy for β-thalassemia Patients

Dr. Suparerk Borwornpinyo

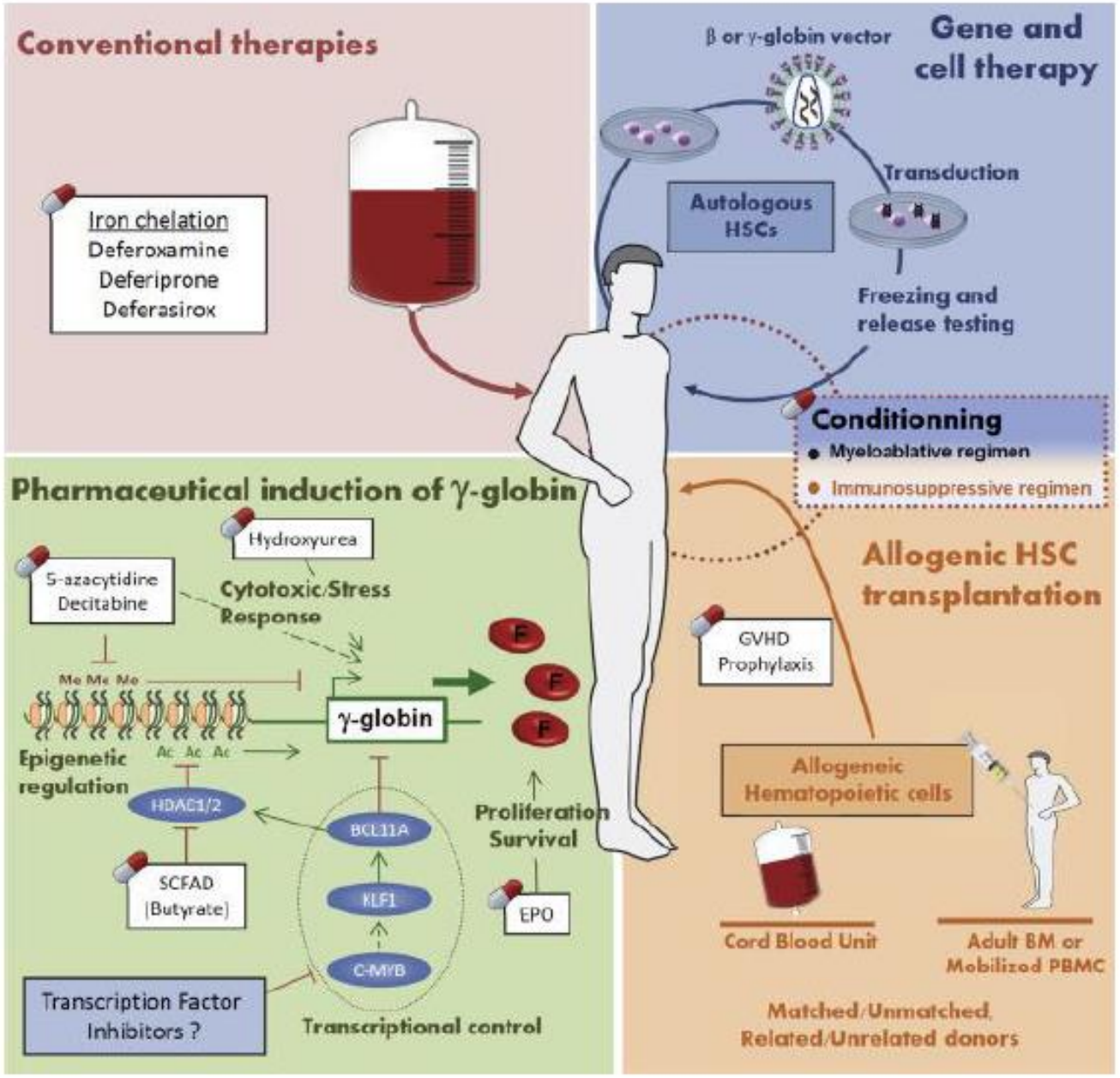
1. Department of Biotechnology, Faculty of Science, Mahidol University, Bangkok, Thailand
2. Excellent Center for Drug Discory (ECDD), Mahidol University, Bangkok, Thailand

The Hope



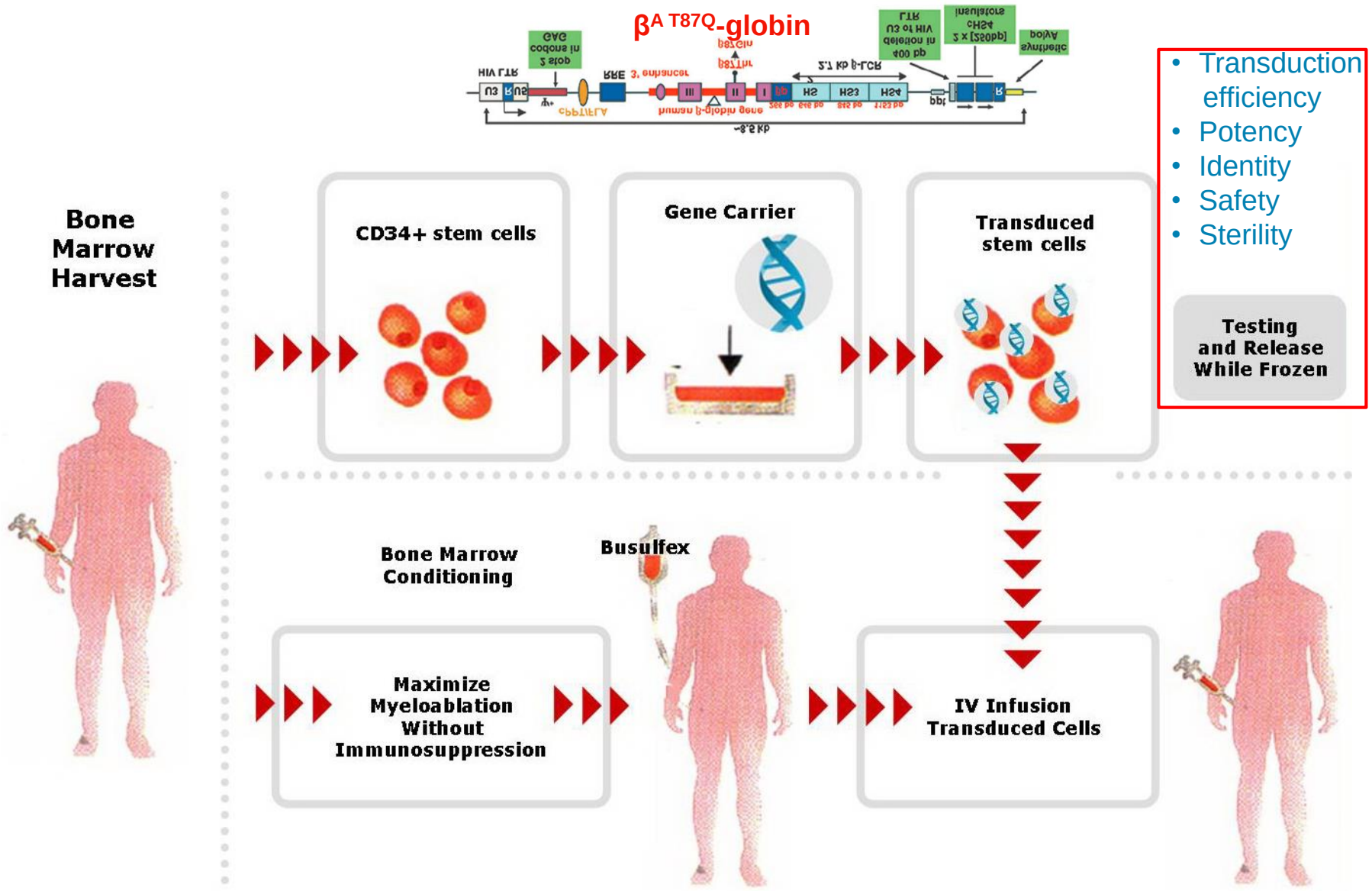
β-thalassemia is highly prevalent, with 80 to 90 million people reported to be carriers across the world (1.5% of the global population).

In Thailand, 10,000 affected infants per year
≈ 3,000 new births / year with beta-thalalassemia major in Thailand
600,000 β-thalassemia patients (1% of Thai population)
50,000 risk couples per year
24 millions of β-thalassemia carriers (40% of Thai population)

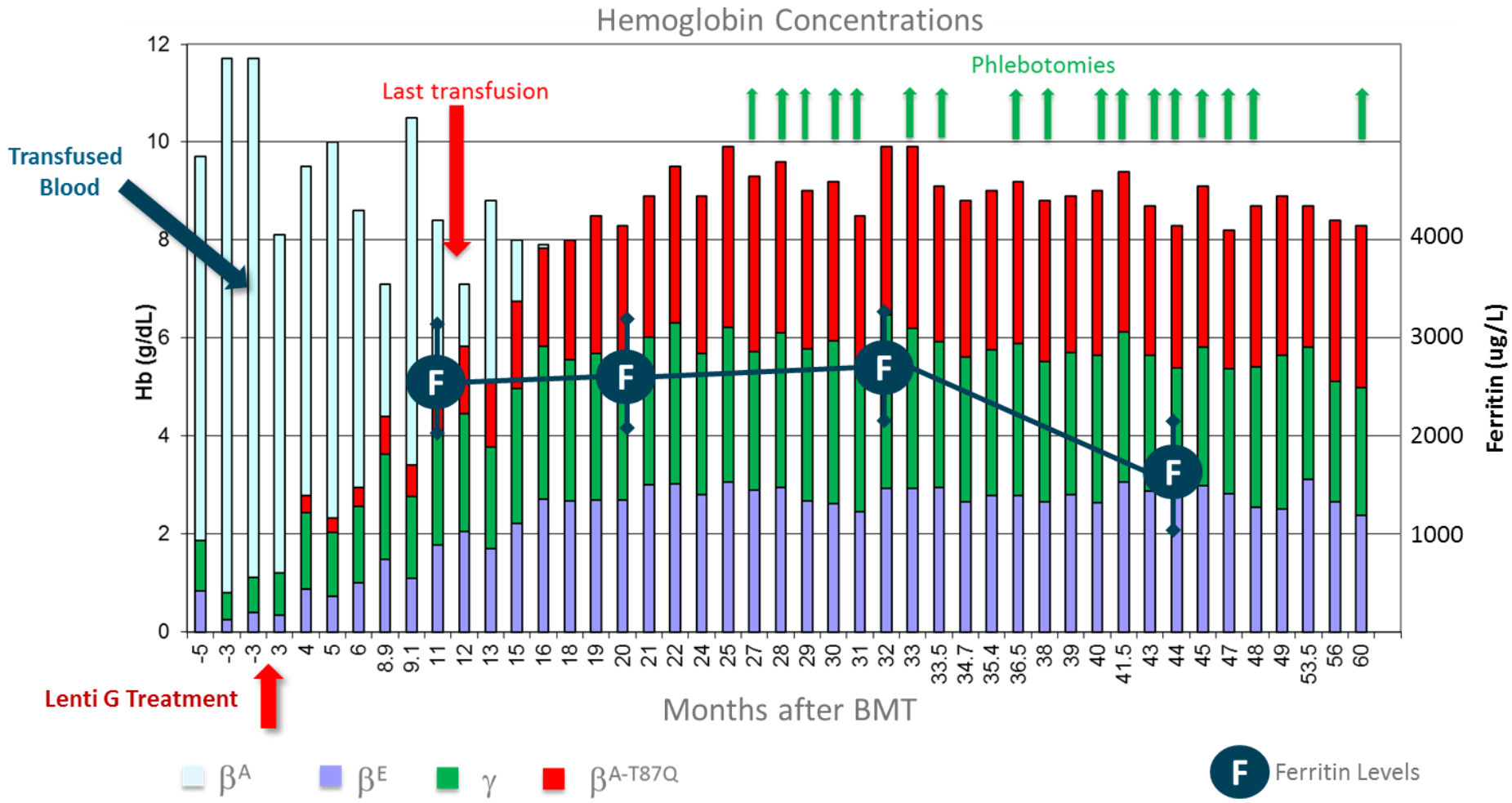


Current and future therapies for beta thalassemia major

Autologous HSC and Gene therapy for the treatment of thalassemia



- Transduction efficiency
- Potency
- Identity
- Safety
- Sterility


Hemoglobin Concentrations
Phlebotomies
Last transfusion
Transfused Blood
Lenti G Treatment
Hb (g/dL)
Ferritin (ug/L)
Months after BMT
βA
βE
γ
βA-T87Q
F
Ferritin Levels

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. Payen, M. Semeraro, D. Moshous, F. Lefrere, H. Puy, P. Bourget, A. Magnani, F. Suarez, F. Monpoux, V. Brousse, C. Poirot, C. Brouzes, J.-F. Meritet, C. Pondarre, T. Lefebvre, D.T. Teachey, U. Anurathapan, P.J. Ho, C. von Kalle, M. Kletzel, E. Vo, O. Negre, R.W. Ross, D. Davidson, A. Petrusich, L. Sandler, M. Asmal, O. Hermine, S. Hacein-Bey-Abina, S. Blanche, P. Leboulch, and M. Cava

ABSTRACT

BACKGROUND

Donor availability and transplantation-related risks limit the broad use of allogeneic hematopoietic-cell transplantation in patients with transfusion-dependent β-thalassemia. After previously establishing that lentiviral transfer of a marked β-globin ($\beta^{A\text{-}T87Q}$) gene could substitute for long-term red-cell transfusions in a patient with β-thalassemia, we wanted to evaluate the safety and efficacy of such gene therapy in patients with transfusion-dependent β-thalassemia.

METHODS

In two phase 1–2 studies, we obtained mobilized autologous CD34+ cells from 22 patients (12 to 35 years of age) with transfusion-dependent β-thalassemia and transduced the cells ex vivo with LentiGlobin BB305 vector, which encodes adult hemoglobin (HbA) with a T87Q amino acid substitution (HbA^{T87Q}). The cells were then reinfused after the patients had undergone myeloablative busulfan conditioning. We subsequently monitored adverse events, vector integration, and levels of replication-competent lentivirus. Efficacy assessments included levels of total hemoglobin and HbA^{T87Q}, transfusion requirements, and average vector copy number.

RESULTS

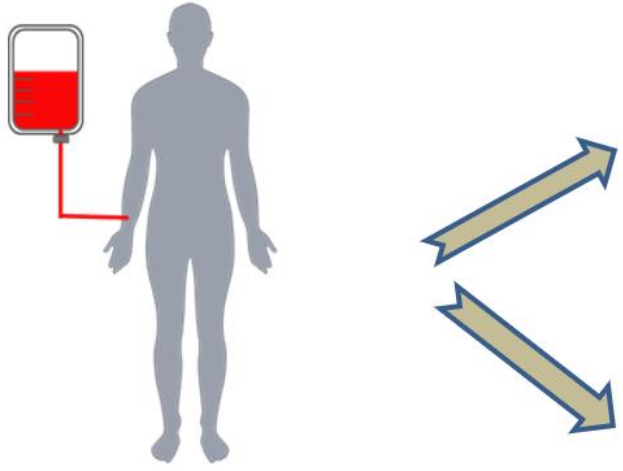
At a median of 26 months (range, 15 to 42) after infusion of the gene-modified cells, all but 1 of the 13 patients who had a non-β^0/β^0 genotype had stopped receiving red-cell transfusions; the levels of HbA^{T87Q} ranged from 3.4 to 10.0 g per deciliter, and the levels of total hemoglobin ranged from 8.2 to 13.7 g per deciliter. Correction of biologic markers of dyserythropoiesis was achieved in evaluated patients with hemoglobin levels near normal ranges. In 9 patients with a β^0/β^0 genotype or two copies of the IVS1-110 mutation, the median annualized transfusion volume was decreased by 73%, and red-cell transfusions were discontinued in 3 patients. Treatment-related adverse events were typical of those associated with autologous stem-cell transplantation. No clonal dominance related to vector integration was observed.

CONCLUSIONS

Gene therapy with autologous CD34+ cells transduced with the BB305 vector reduced or eliminated the need for long-term red-cell transfusions in 22 patients with severe β-thalassemia without serious adverse events related to the drug product. (Funded by Bluebird Bio and others; HGB-204 and HGB-205 ClinicalTrials.gov numbers, NCT01745120 and NCT02151526.)

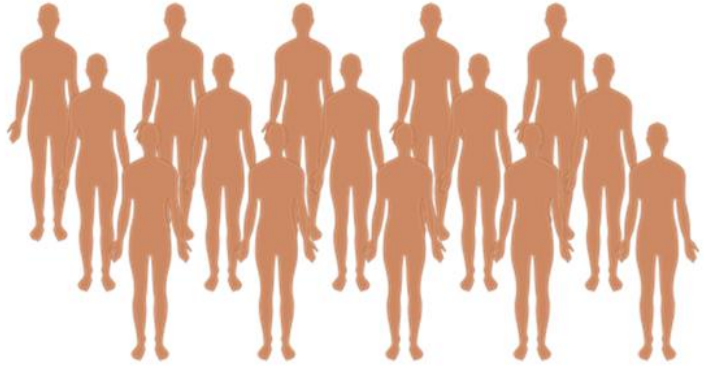
Multicenter phase 1-2 study (since 2013)
Ages 12- 35

The success of gene therapy

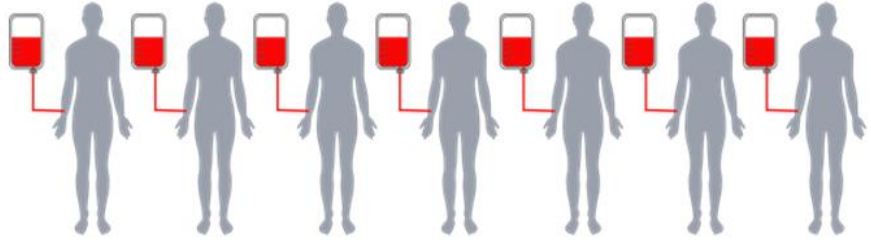


22 patients
with transfusion-dependent
β-thalassemia

Normal hemoglobin levels, No transfusion (but one)



13 patients



9 patients

Reduced number and volume of transfusions

(Thompson et. al., 2018)

โลหิตจางธาลัสซีเมียและค่าใช้จ่ายสำหรับการรักษาในประเทศไทย

โรคพันธุกรรมที่**พบมากที่สุดในโลกและในประเทศไทย**

พยาธิสภาพ: เม็ดเลือดแดงมีอายุสั้น
อาการและอาการแสดง: ซีด ตับม้ามโต หน้าตาเปลี่ยนแปลง

- **รับเลือดและยาขับเหล็กตลอดชีวิต**

  ประมาณ 12 ล้านบาท (จนถึงอายุ 30 ปี)

- **ปลูกถ่าย stem cells**

  ประมาณ 2-5 ล้านบาท

- **ยีนบำบัด (gene therapy)**

  อยู่ในขั้นตอนการวิจัย

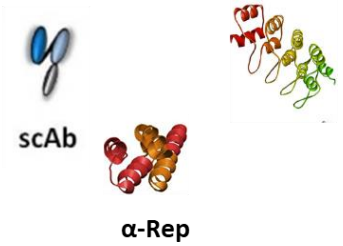
มะเร็งเม็ดเลือดขาวและค่าใช้จ่ายสำหรับการรักษาในประเทศไทย

- ในแต่ละปีพบผู้ป่วยมะเร็งเม็ดเลือดขาวมากกว่า **5000** คน
- ค่าใช้จ่ายในการรักษาประมาณ **1 - 3** ล้านบาท ต่อคน
- ประมาณ **10% (500** คน**)** เกิดโรคกลับ **(relapse)**ไม่มียารักษา

การรักษาด้วยภูมิคุ้มกันบำบัดเพื่อการรักษาโรคมะเร็ง: Immunotherapy Platform

Target Identification

Phage displays:
scFV
Ankyrin
Alpha-repeat protein



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CD19, GD2

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Anti-GD2-Anti-CD3

→ Radioimmunotherapy (RIT)

Targeted Cancers

Pediatric and young adult acute lymphoblastic leukemia (ALL)
Large B cell non-Hodgkin's Lymphoma
Solid tumor: neuroblastoma

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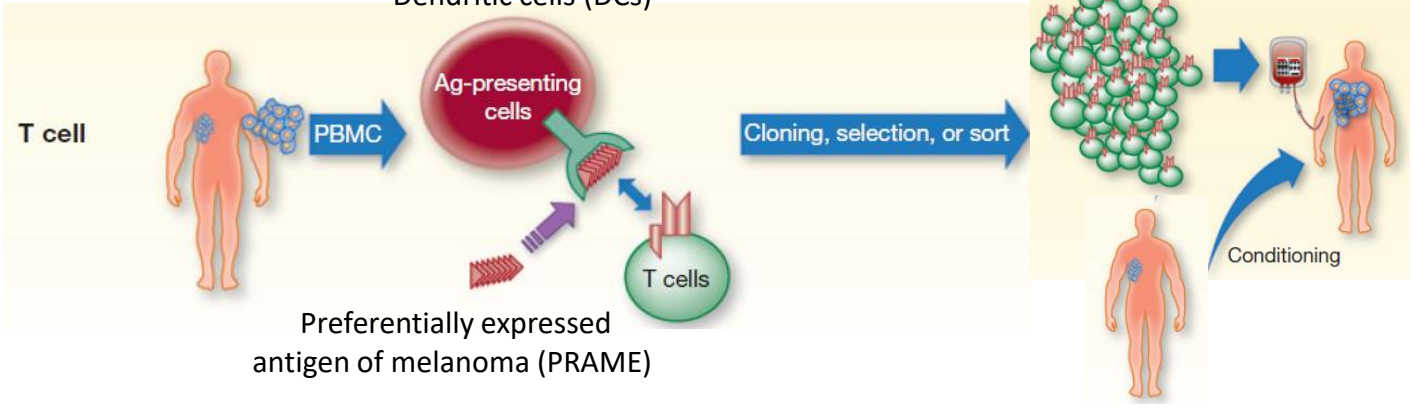
Adoptive T-cellular therapy

Antigen-specific
T-cell enrichment

Dendritic cells (DCs)



Preferentially expressed
antigen of melanoma (PRAME)

Melanoma
Chromic myeloid leukemia (CML)
Acute myeloid leukemia (AML)

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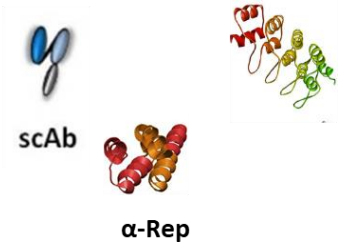

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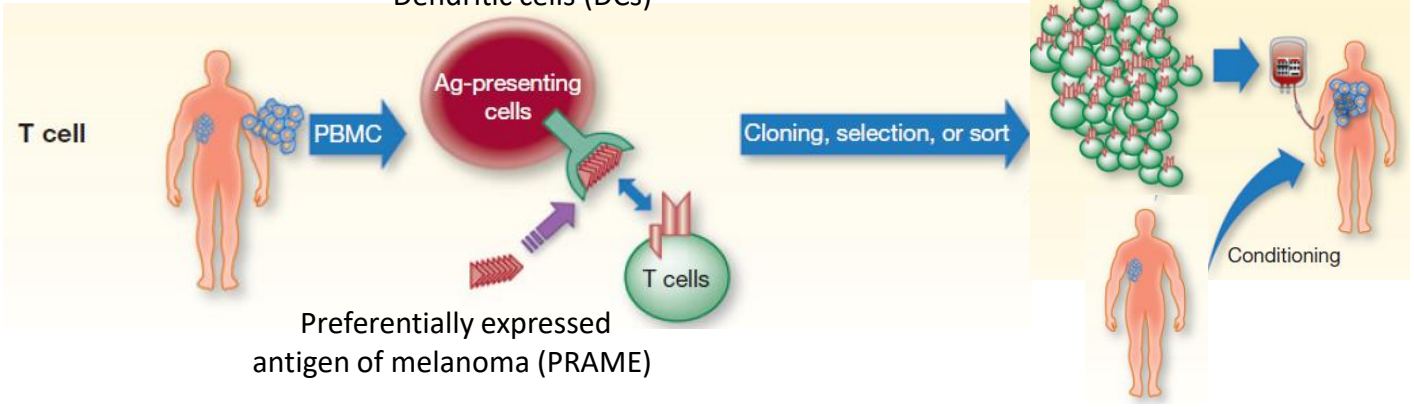

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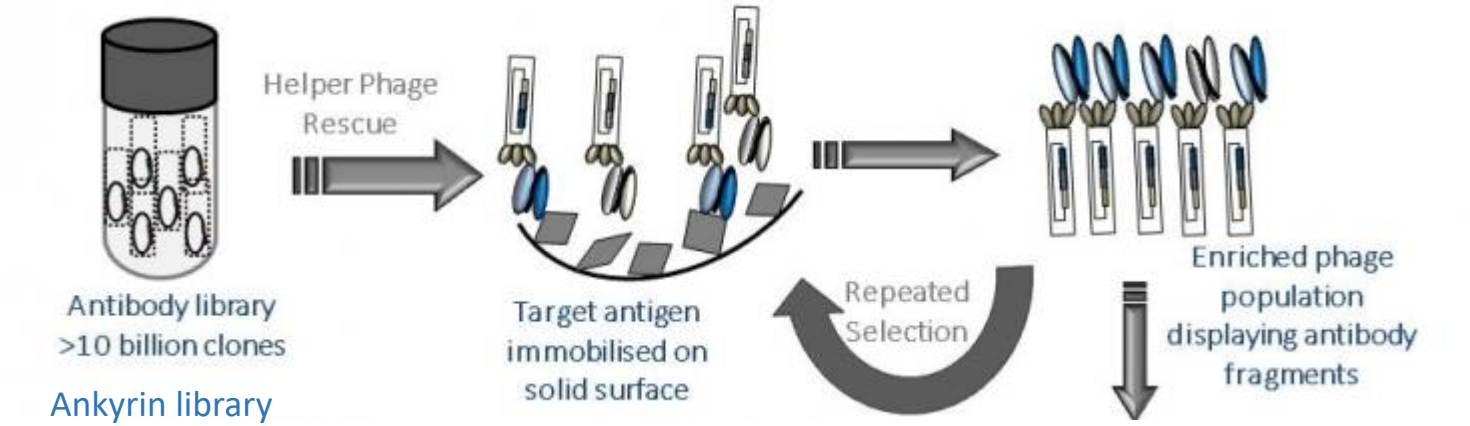
ศ.ดร. วันเพ็ญ ชัยคำภา

รศ. ดร. นิทัศน์ สุขรุ่ง

ผศ. ดร. สาวิตรี นะงอลา

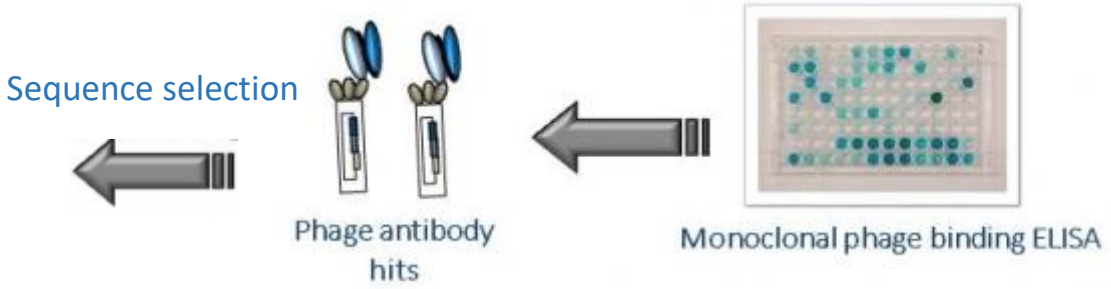
Phage display technology



Ankyrin library

Alpha Rep library

ARPins



https://www.abdn.ac.uk/sbf/technology/phage-display/

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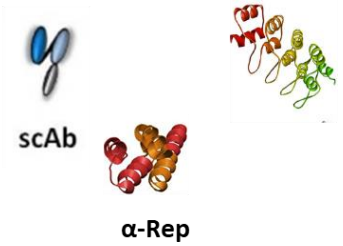

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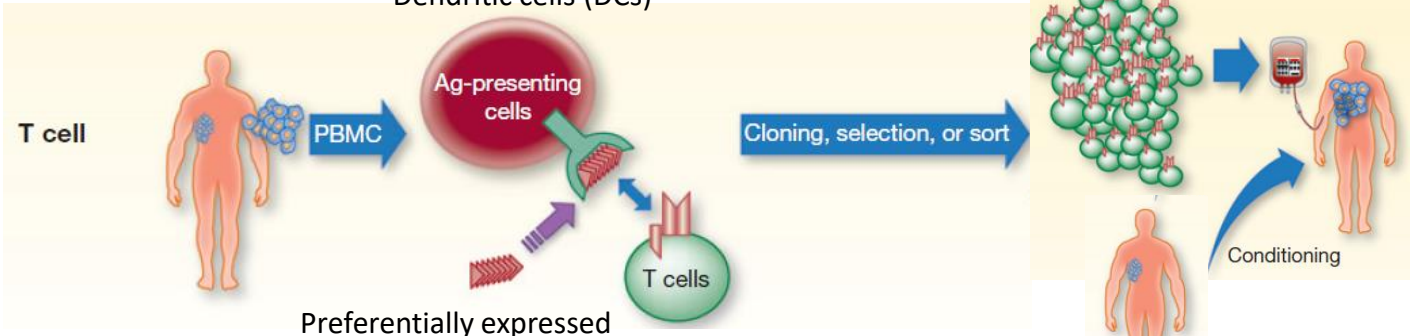

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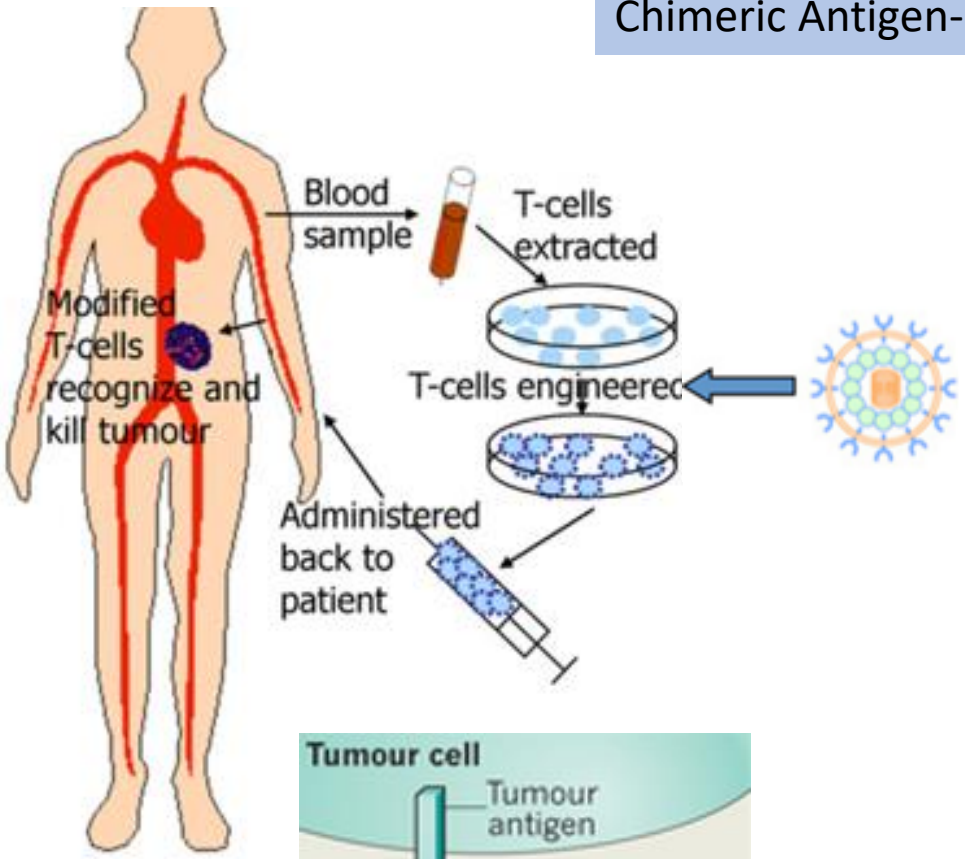

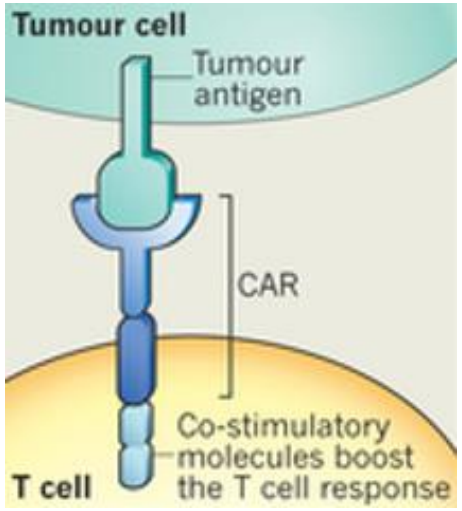

รศ.นพ. อุษณรัสมิ์ อนุรัฐพันธ์
ดร. สมศักดิ์ ประสงค์ธนกิจ
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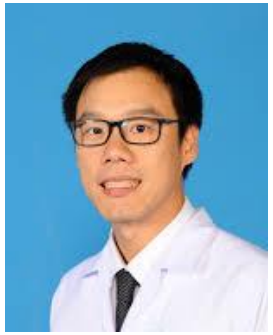

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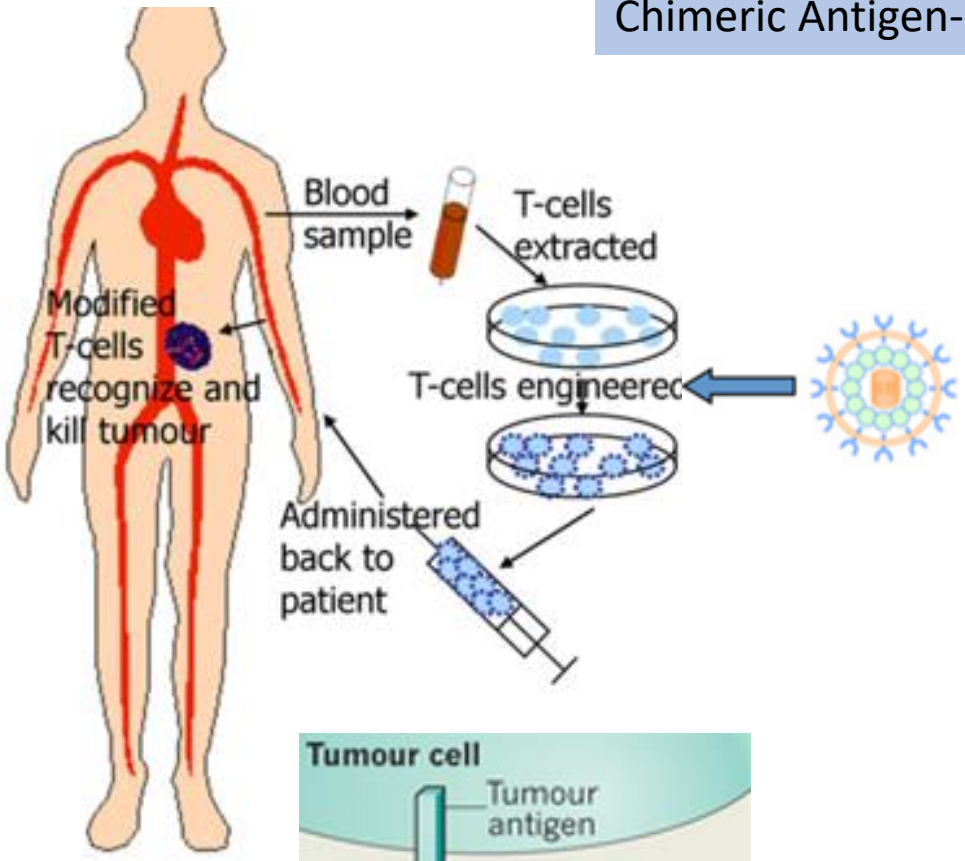

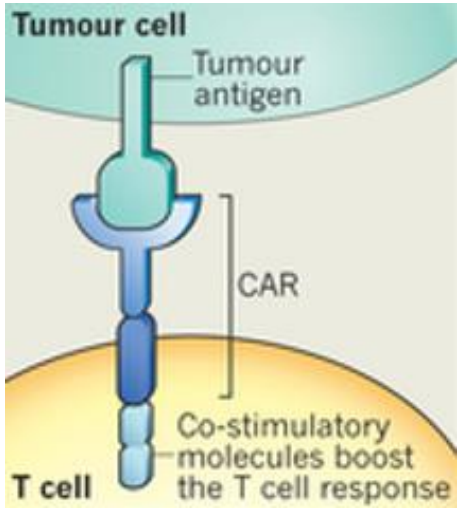

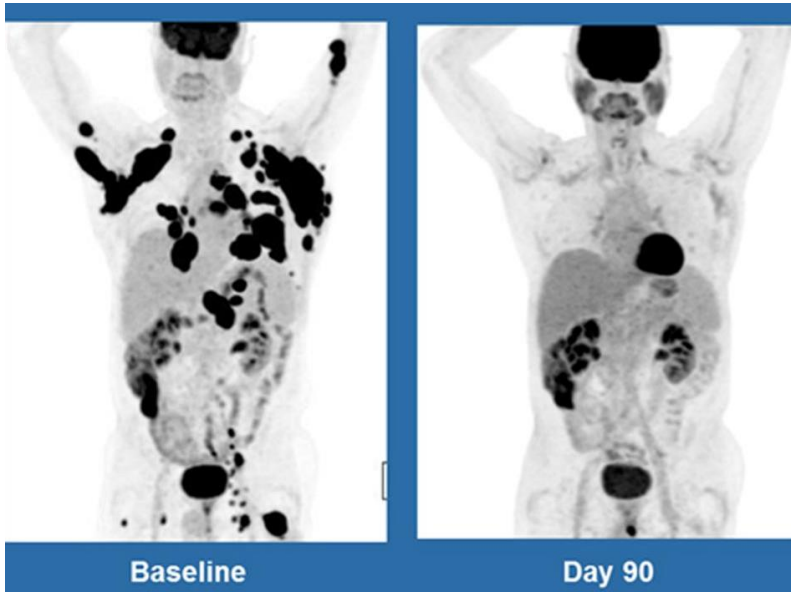

These scans show a 62-year-old man with non-Hodgkin lymphoma, at left in December 2015, and three months after treatment with Kite Pharma's experimental gene therapy at MD Anderson Cancer Center in Houston

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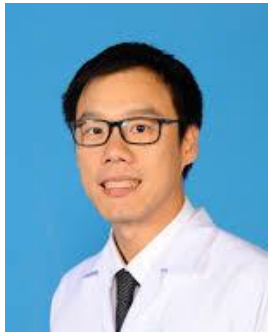

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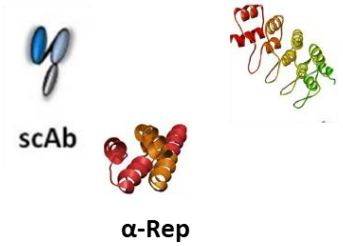

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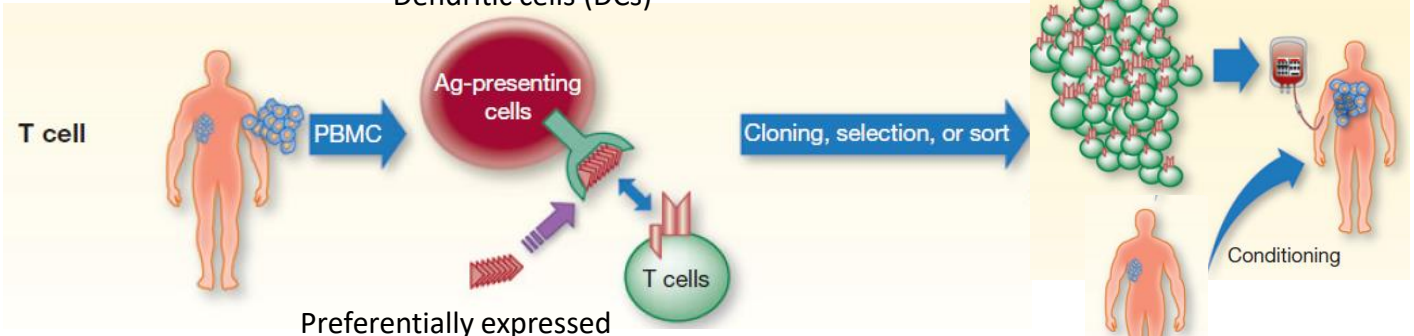

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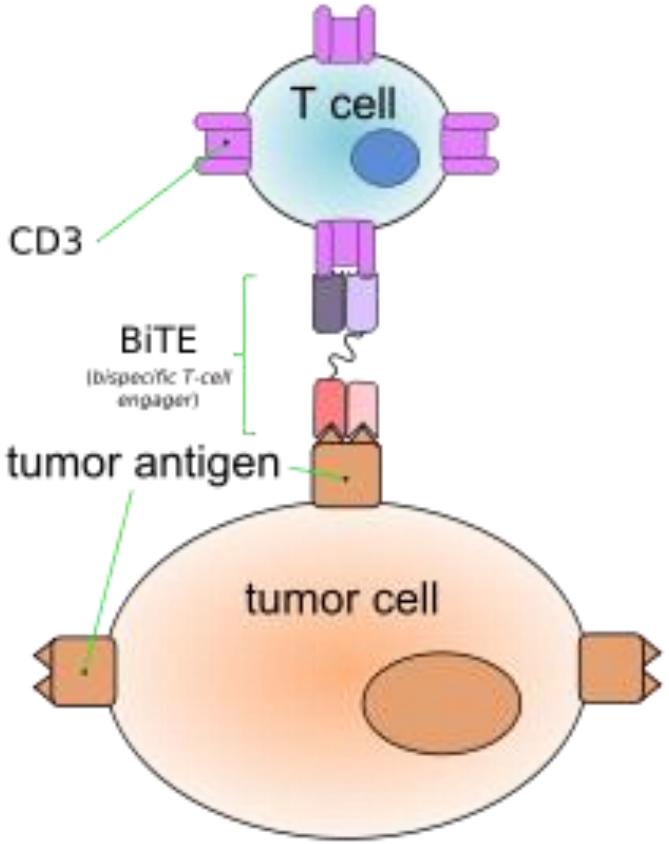
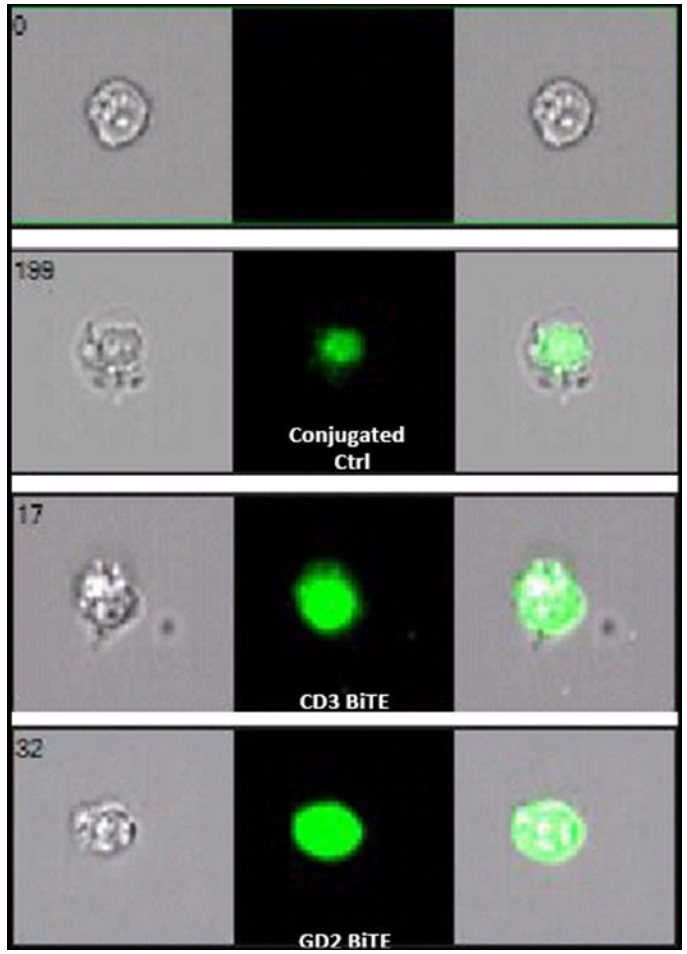
ดร. ศรินทิพย์ ปรีดาเกษมสิน

Bi-specific T-cell engagers (BiTEs)





Representative imaging flow cytometry analysis of binding of purified BiTEs on GD2-positive neuroblastoma SHSY-5Y cells

ผศ. ดร. กุลธิดา กิติดี
ดร. ศรินทิพย์ ปรีดาเกษมสิน

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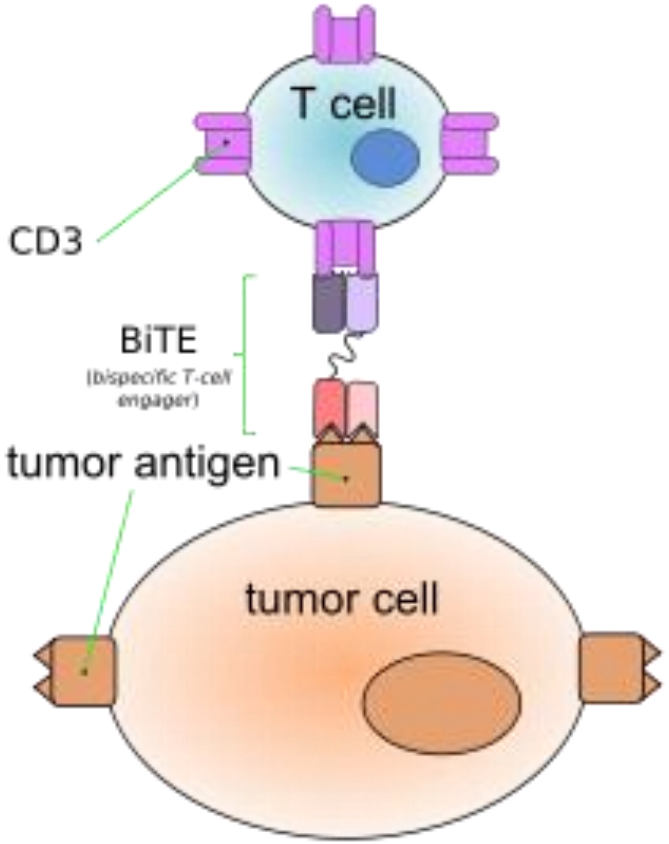
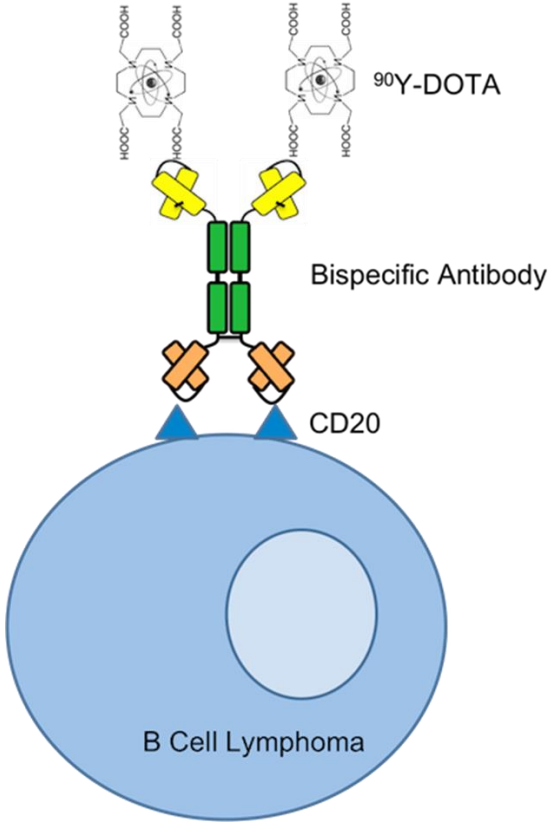


Radioimmunotherapy (RIT)



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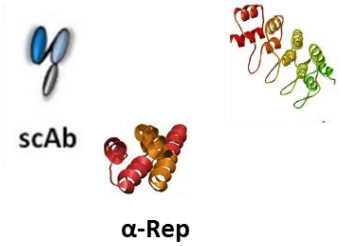

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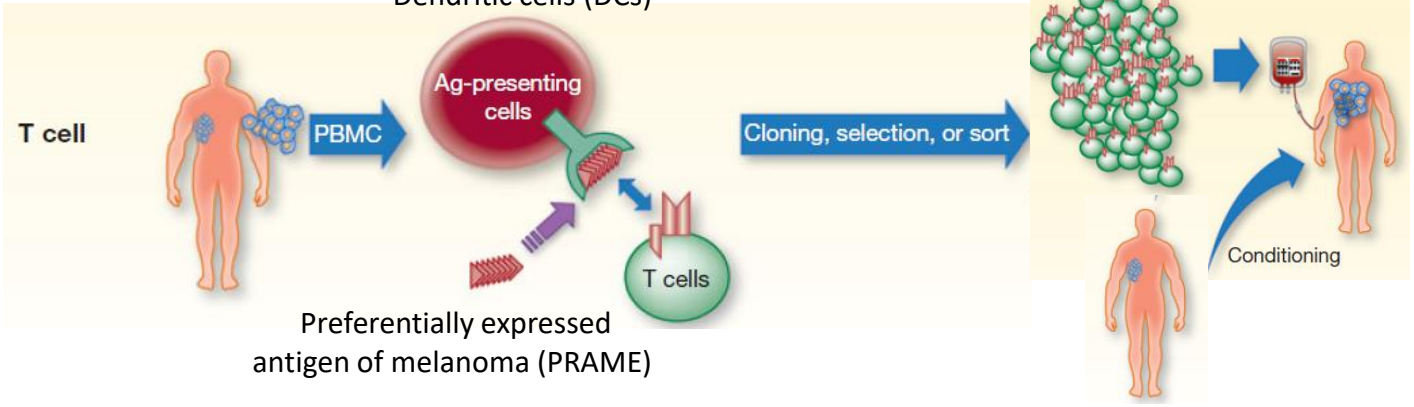
Adoptive T-cellular therapy

Antigen-specific
T-cell enrichment

Dendritic cells (DCs)



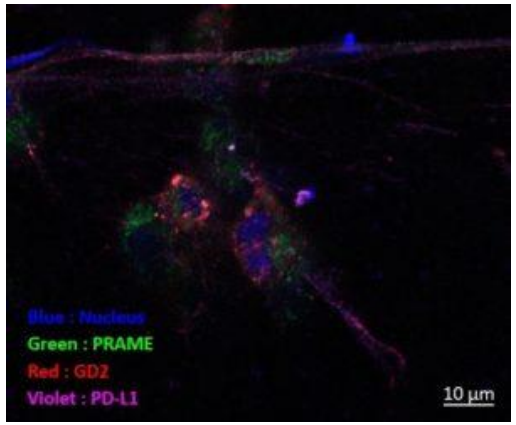
Preferentially expressed
antigen of melanoma (PRAME)

Melanoma
Chromic myeloid leukemia (CML)
Acute myeloid leukemia (AML)

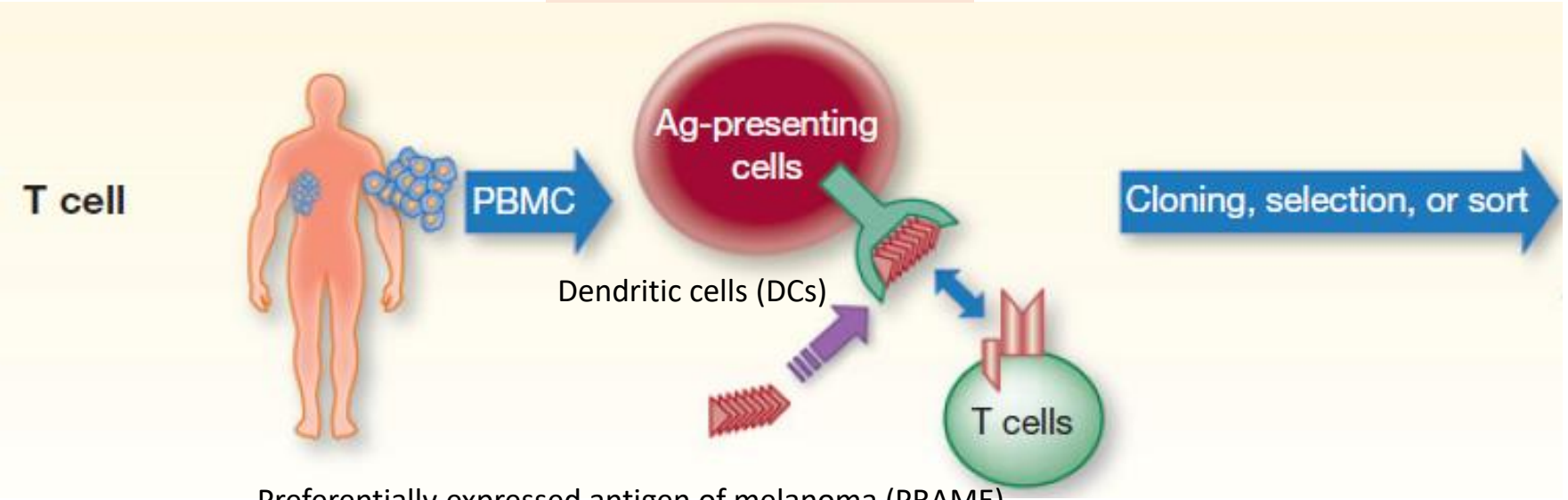
ดร. สว่าง เพชรวิเศษ
นาย วสุพล ผกามาศ
นส. พรประภา ศรีหมอกอุ่น

ผศ. นพ. กิติพงศ์ สุนทราภา
นาย ชัยพิชิต พยังเค
นส. พรรณวดี เปลื้องนุช
นส. พรภิมล เอกอุดมสุข

Adoptive T-cellular therapy

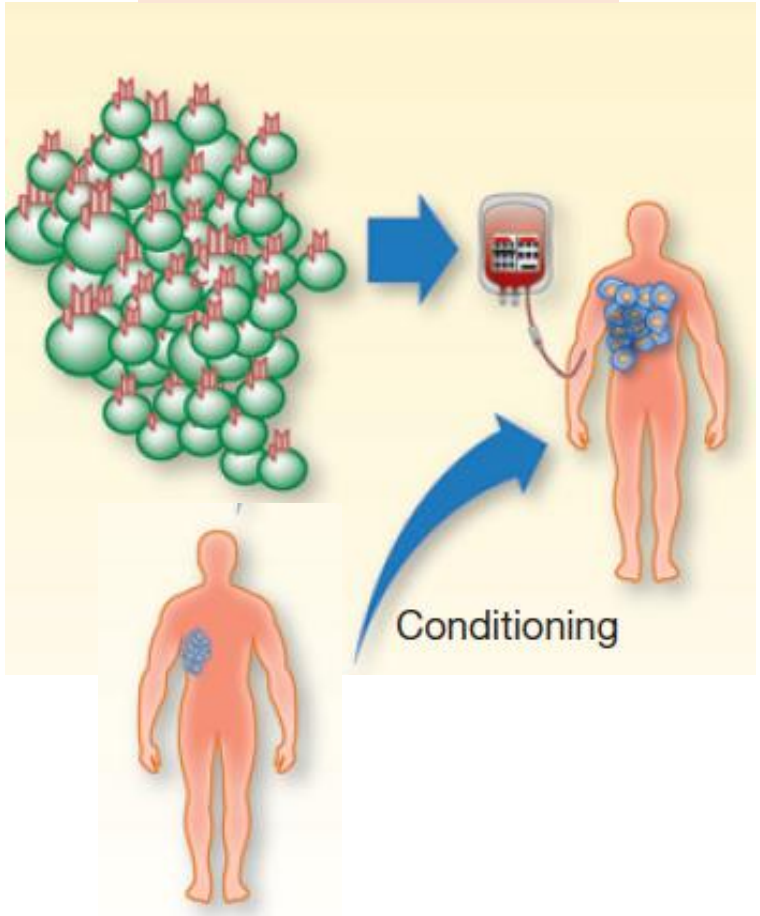


Antigen-specific T-cell enrichment



Preferentially expressed antigen of melanoma (PRAME)

T-cell expansion and infusion



Clin Cancer Res; 19(17) September 1, 2013

มหาวิทยาลัยมหิดล
Mahidol University
Wisdom of the Land

Establishment of a Medical Hub for Cell and Gene Therapy in Thailand

Prof. Suradej Hongeng, M.D.

Has the Era of Gene Therapy Finally Arrived?

NOVARTIS Our Work About Us News Investors

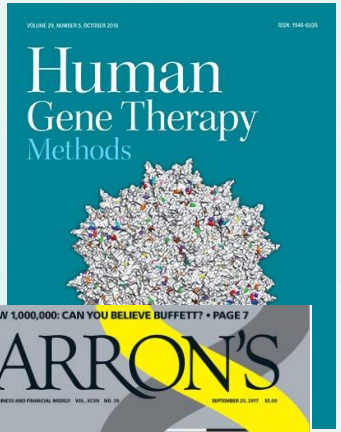
Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice

475,000 US$

August, 2017

Early 2019

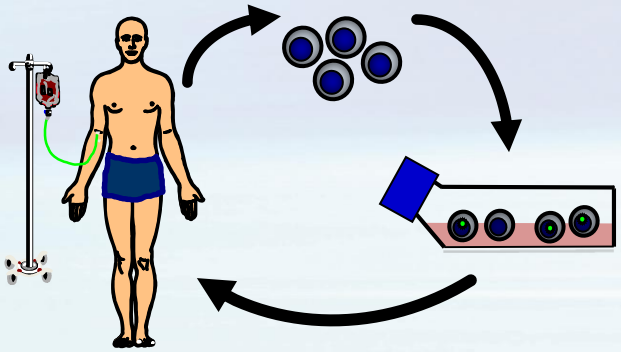
Novartis says $4m price is reasonable for SMA gene therapy



Portfolio of Products

1. Thalassemia Treatment

Majority of patients are in Asia - approximate 200,00-300,000 patients in Thailand
≈ 3000 new births / year with beta-thalassemia major in Thailand

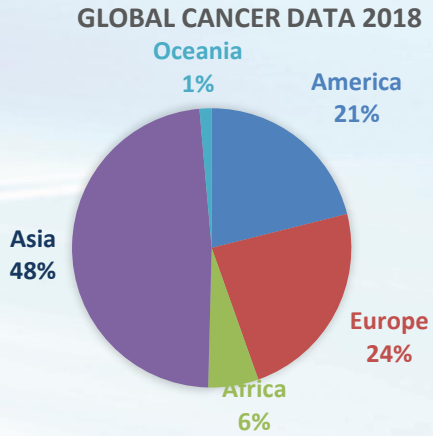


Technology is unique

- No need stem cell donor
- Treatment with Patient ‘s stem cell (No one has done this before)
- No need Immunosuppressor
- Permanent and one time treatment

2. CAR-T cells – Leukemia

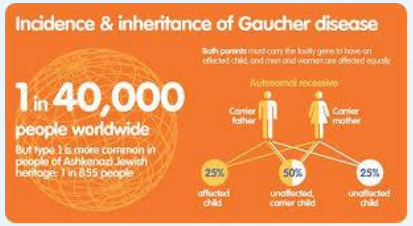
- developed CAR T- Leukemia by Prof. Suradej and Rama hospital
- Ready to commercialize in near future 2019
- Current treatment cost of Novartis ‘s CAR-T is around 500,000 USD/ shot



Source: WHO

3. Gaucher Disease (rare genetic disorder caused by deficiency of enzyme cells)

- Similar Vector Platform to Thalassemia, easy to develop along with Thalassemia
- Gaucher disease affects up to 1 in 40,000 live births in the general population.
- Currently Thai government subsidizes 5 patients in Thailand at Rama hospital



Gene Therapy: Business Model / Medical Hub

1 Patients consult doctor at hospital

2 Cells are removed from the patients

3 Hospital delivers cells to the lab

NEW Co. Scope
Vector & Process

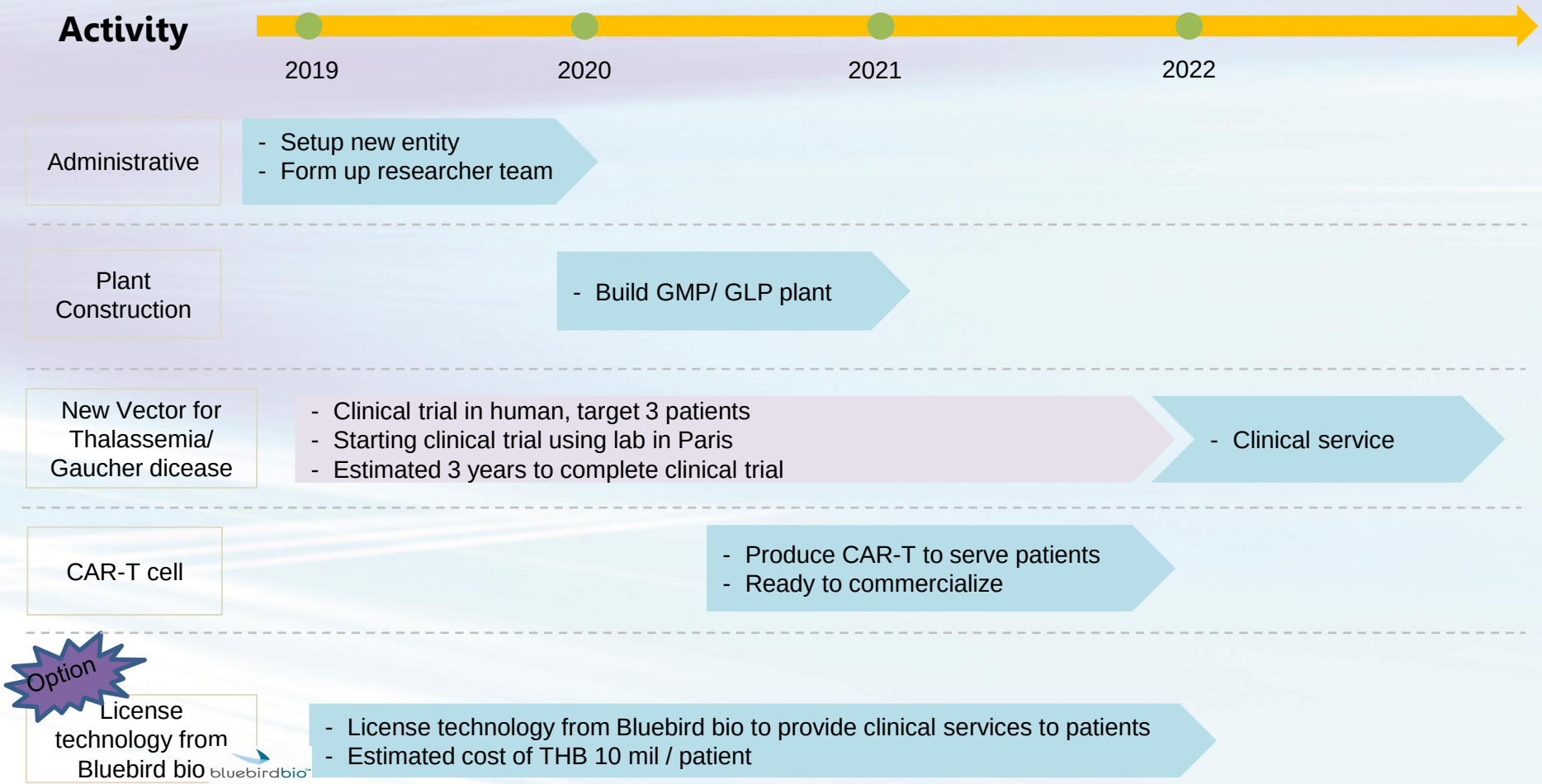
4
- In the laboratory, a therapeutic gene is designed and engineered into the vector.
- The engineered vector is then mixed with patients' T lymphocytes (T-cells).
- The T cells from the patient thus became genetically modified CAR-T cells.

"Living Drug Product"

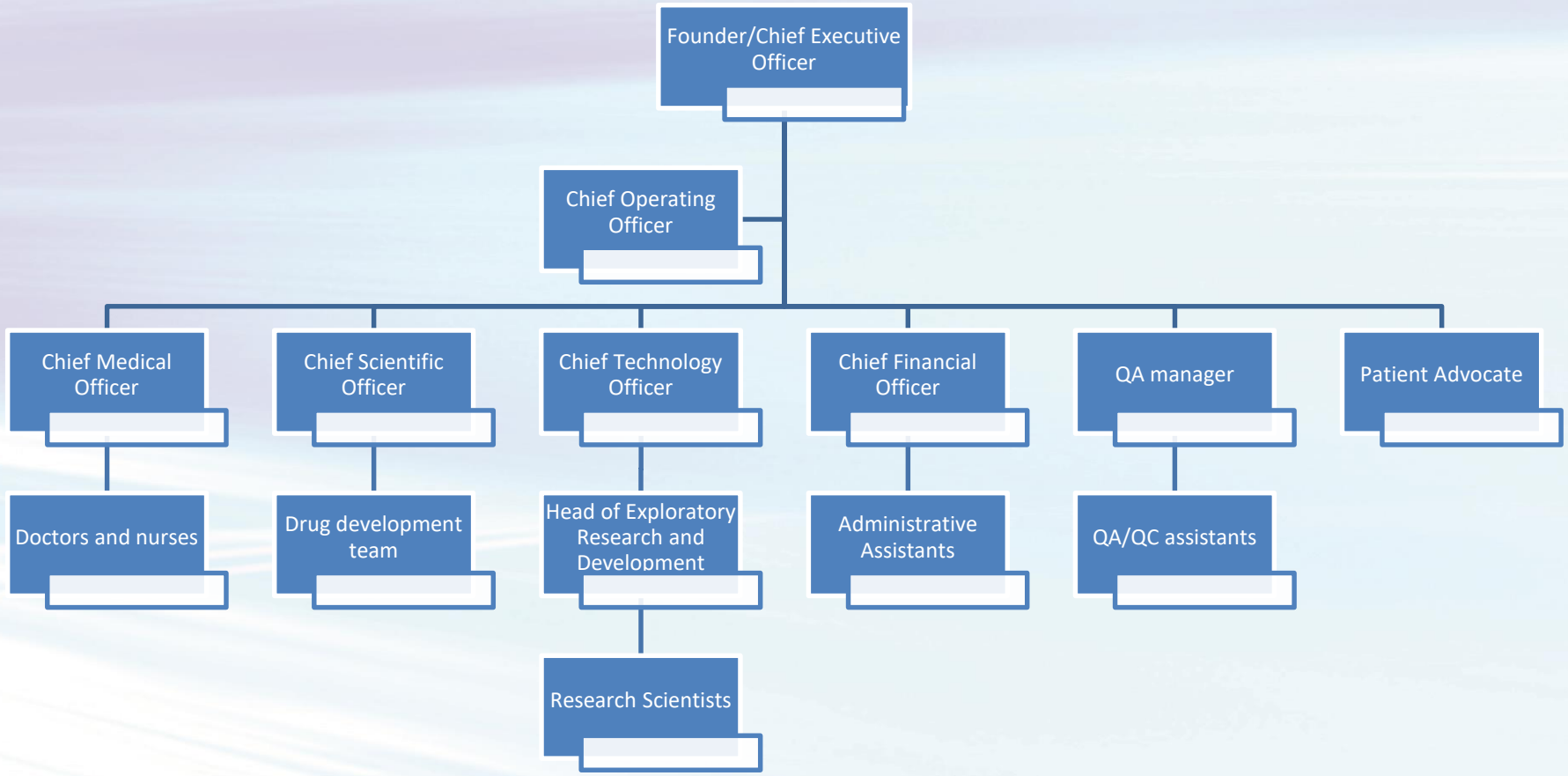
5 Deliver back to the hospital

6 The altered cells are reinjected into the patients

Milestones: Timing - competitiveness



Organizational Chart



Infrastructure milestone (manufacturing)

Clinical trial (mass production of the vectors): FROM LAB TO PATIENTS

Budget: TBD Budget: TBD Budget: TBD Budget: TBD

Tentative Total time: 1 years and 3 months

*Starting from financial closure

Infrastructure milestone (Laboratory)

Exploratory and discovery phase for new technology and advancement in gene therapy in other genetic disorders

Budget: TBD Budget: TBD Budget: TBD Budget: TBD

Tentative Total time: 1 years and 1 month

*Starting from financial closure

Value Proposition

500,000 US$

50,000 US$
(10 times less)

คุณภาพระดับโลก
ประสิทธิภาพสูง
ปลอดภัยสูง
ทุกคนเข้าถึง


THANK YOU