งานวิจัย ATMPs สู่การใช้งานทางคลินิกและการบริการในโรงเรียนแพทย์
ATMPs Research into Clinical Applications and Services in Medical Schools

อ.นพ.ภรมิษฐ์ ศุภพิพัฒน์

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ประวัติการทำงาน:

หัวหน้ากลุ่มวิจัยเซลล์บำบัดมะเร็ง ศูนย์ความเป็นเลิศด้านภูมิคุ้มกันบำบัดมะเร็ง คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

Education

- 2011-2012 Pediatric leukemia and hematopoietic stem cell transplantation fellowship, Texas Children Hospital, Baylor College of Medicine, Houston, Texas, US
- 2008-2011 Pediatric hematology and oncology fellowship, , Texas Children Hospital, Baylor College of Medicine, Houston, Texas, US
- 2005-2008 Pediatric Residency, Cook County Children Hospital, Chicago, Illinois, US
- 2002 Doctor of Medicine (MD) Chulalongkorn University, Bangkok, Thailand

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Development of Point-Of-Care/Non-viral platform for sustainable CAR-T cell Therapy in Thailand

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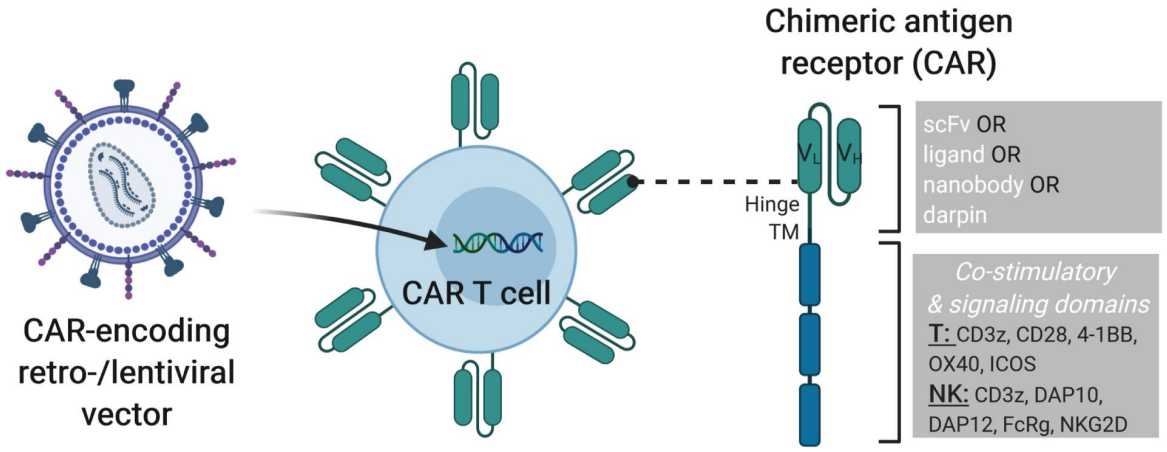
Director, Cellular Immunotherapy Research Unit

Medical Director, Cell and Gene Therapy Manufacturing Center

Chimeric Antigen Receptor T cell

- Chimeric Antigen Receptor T cell (CAR T cell) can cure 50-80% of blood cancer
- Cost per dose of commercial CAR T cell is 10-15 million THB
  - Complex manufacturing
  - High cost for GMP grade viral vector and QC related to virus



Abecma (idecabtagene vicleucel) Suspension for IV infusion

Breyanzi (lisocabtagene maraleucel) Suspension for IV infusion

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

Commercialization faces major challenges on the CAR T patient journey.

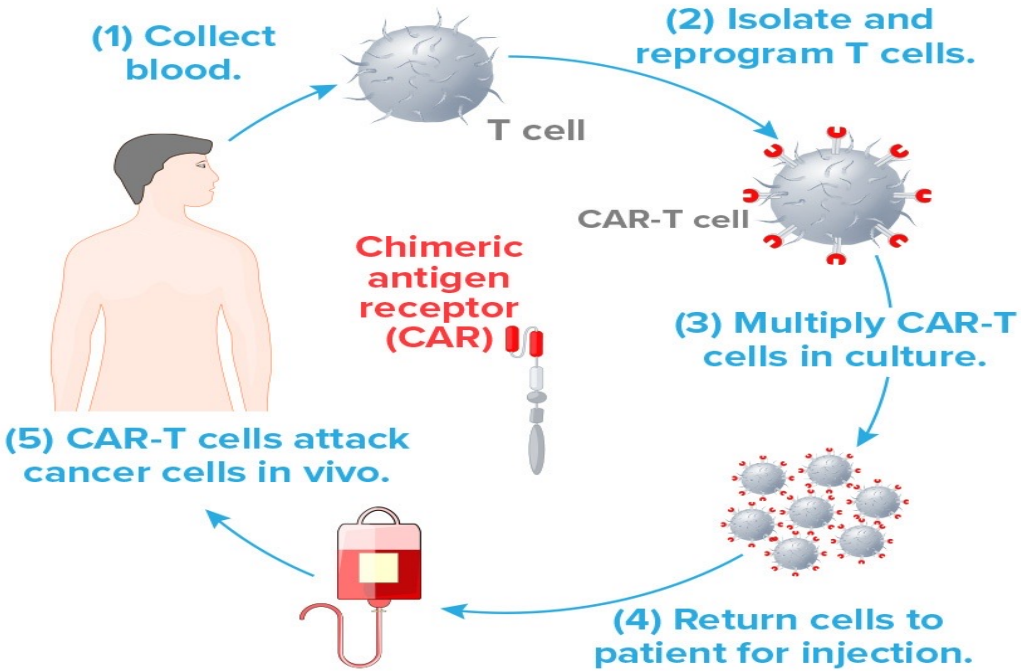
Patient journey	Patient referral and entry	Patient eligibility	Leuka-pheresis	Conditioning therapy	CAR T creation and expansion	CAR T infusion	Monitoring
	Patient qualifies and is referred to a CAR T physician	Patient undergoes pretreatment eligibility assessment	Peripheral blood mononuclear cells undergo apheresis and are shipped to a manufac-turing facility	Patient undergoes conditioning chemo-therapy during cell processing	CAR T-encoding genetic material is transferred via viral vector—CAR T cells are then expanded	CAR T cells are administered to patient following lympho-depletion	Patient is closely monitored with a long-term follow-up plan

Top three challenges

Complex manufacturing and supply chain
- Centralized manufacturing, low economies of scale, high cost of goods sold
- Complex cold chain required
- Long vein-to-vein time affecting patient eligibility

High-touch commercial model
- High cost to set up, certify, and scale sites
- Complex center protocols and training requirements

Reimbursement challenges
- Economic uncertainty set by the Centers for Medicare & Medicaid Services policies
- Delayed preapproval reimbursement can impact the patient's CAR T eligibility



Solution:

1. Decentralized manufacturing
2. Developing allogeneic products

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CU strategies for sustainable CAR T cell therapy in Thailand

- Transduction:

  Non-Viral delivery

  Viral vector

- Facility:

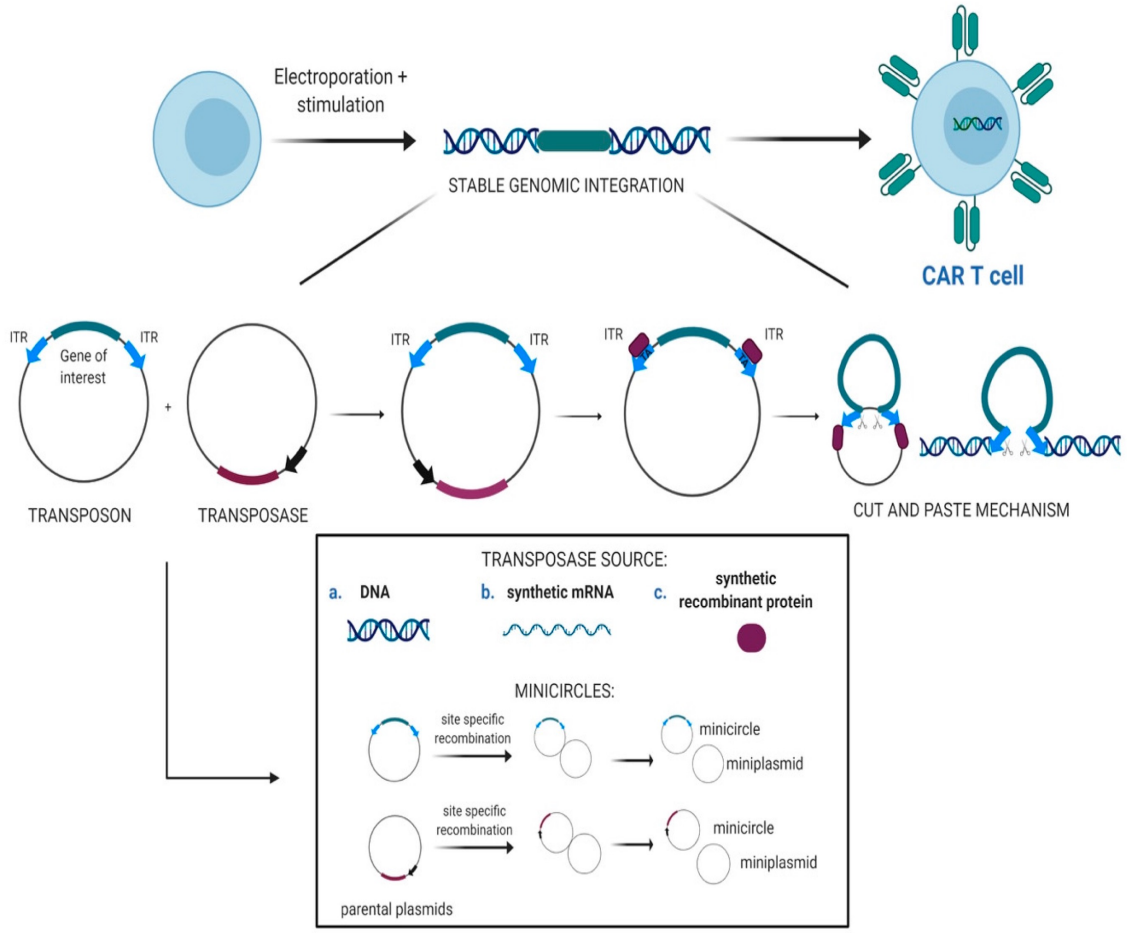
  Point-of-Care processing

  Centralized

Non-viral CAR T cell technology

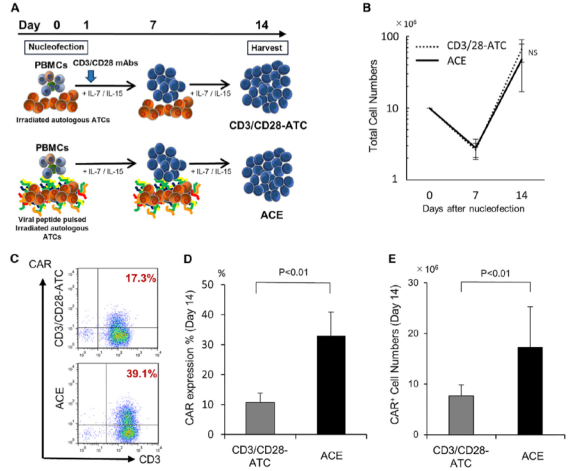
PiggyBac is a sustainable option for T cell engineering

	Viral transduction	PiggyBac transposon system
Transduction method	Viral vector	Electroporation
Cargo size	10-15 kb	200 kb
Gene insertion	Random, risk of mutagenesis	Less random
GMP grade vector cost	300,000 – 1,500,000 THB	10,000 -100,000 THB
Cell processing	More complex	Less complex
Memory CAR T cell (CAR T persistence)	Low	High
Monitoring of Replication competent virus	15 year (US FDA guideline)	N/A



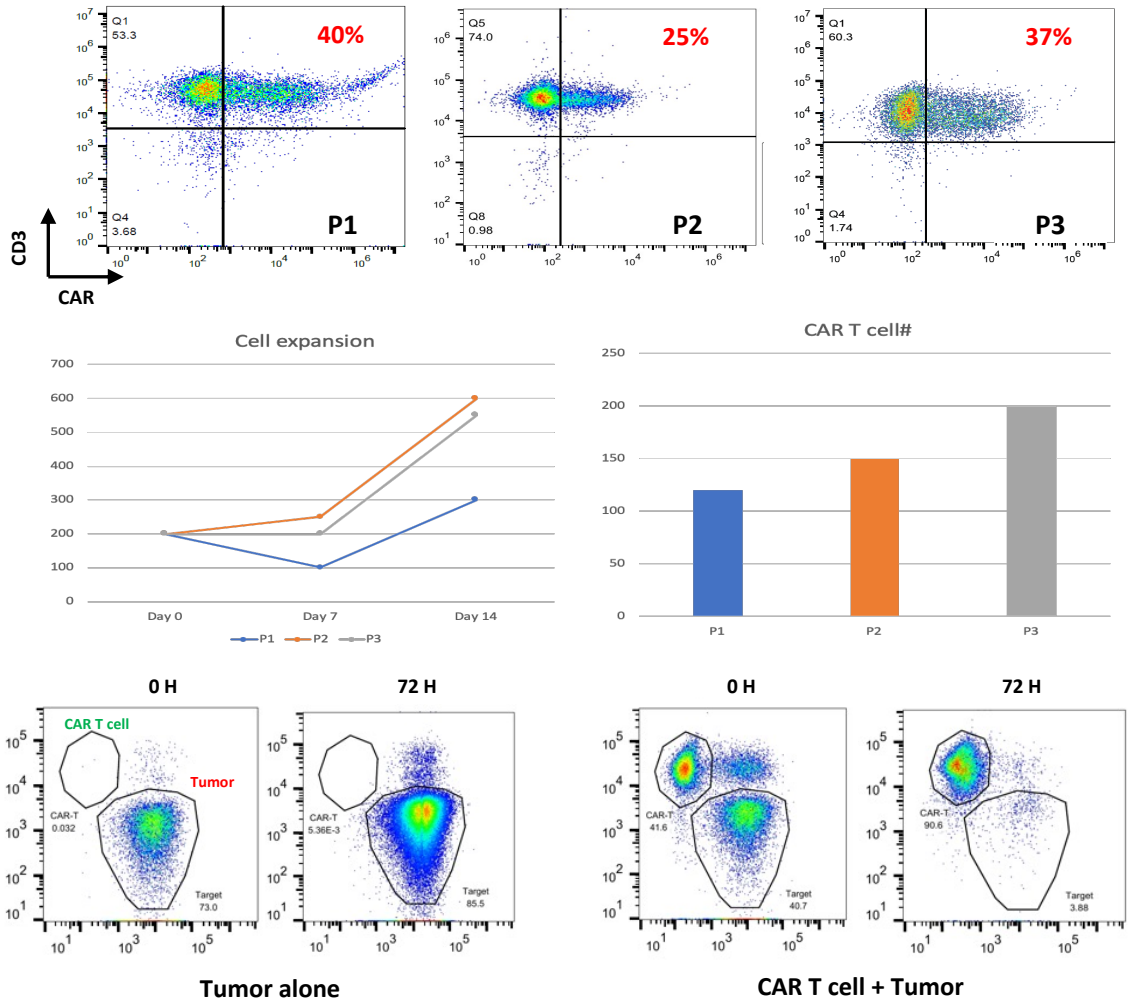
Technology transfer of PB CAR T cell CU-Nagoya University


安価な白血病療法
名大がタイ支援へ
「最先端技術 途上国に広
タイでの実施を目指す
名大によるCAR-T細胞療法
CAR-T細胞を作製
特定のがん細胞を攻撃
CAR-T細胞療法 免疫細胞の一つ「T細胞」を活性化させ、特定のがん細胞を集中的に攻撃する最新の白血病治療法。患者のT細胞を体外に取り出し、遺伝子操作で、がん細胞への攻撃能力の高いCAR-T細胞を作製。増殖させた上で点滴などで患者に投与する。難治性の白血病や、悪性リンパ腫で効果があり、欧米や中国で開発が進んでいる。乳がんや肺がんなど固形がんへの応用も期待されている。
一部の白血病患者向けの治療法「CAR-T（カーティー）細胞療法」を、タイの国立大学病院で実施できるよう、名古屋大医学部が技術支援することが分かった。最先端の治療法で、国内で一月に製造販売が了承された製剤は一回数千万円かかる可能性がある。しかし、名大が研究を進めている技術はコストダウンを売りにしており、経済力の弱い発展途上国での白血病治療の前進にも役立てる。
支援するのは、首都バンコクにあり、名大と学術交流協定を結ぶ国立チュラロンコン大の付属病院。タイ側から要請があり、名大は英訳した作製手順書などを無償提供する。さらに、四月にも現地の技術者二人が来日し、一カ月程度、名大で同細胞
（安田功）



- Nagoya University collaborators:
  - Professor Yoshiyuki Takahashi, MD PhD
  - Assistant Professor Nobuhiro Nishio, MD PhD
- ACE method PiggyBac CD-19 CAR T transduction and expansion
- Two scientists training for PiggyBac CAR T cell manufacturing June to July 2018
- Improve transduction efficiency from 5-10% to 40-80%
- IRB approval December 2019
- Clinical Trial Phase I Site initiation July 2020

Protocol validation: Clinical scale production in Thailand

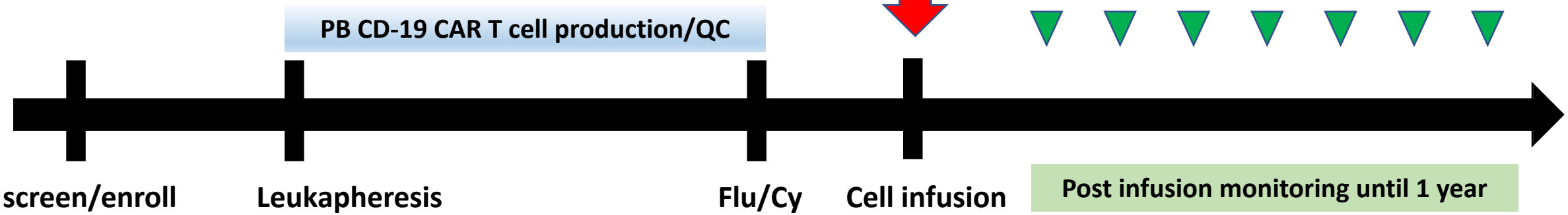


- Healthy donor (N =3)
- PBMCs on day 0 = 200x10e6 cells
- Final products on day 14:
  - Total cell number 300 to 600x10e6 cells
  - CAR T cell efficiency 25-40%
  - Absolute CAR T cell numbers: 125 -200x10e6 cells
  - Standard CAR T dosage (1x10e6 cells/kg): 60-80x10e6 cells
- CAR T cell activity
  - > 90% Inhibition ratio to ALL cell line

PB-CD-19 CAR T cell clinical protocol

- **Inclusion criteria**
  - R/R ALL and NHL
  - CD19 +
  - 18-60 y/o
  - Male and female
  - ECOG = 0-2
  - Normal organ function

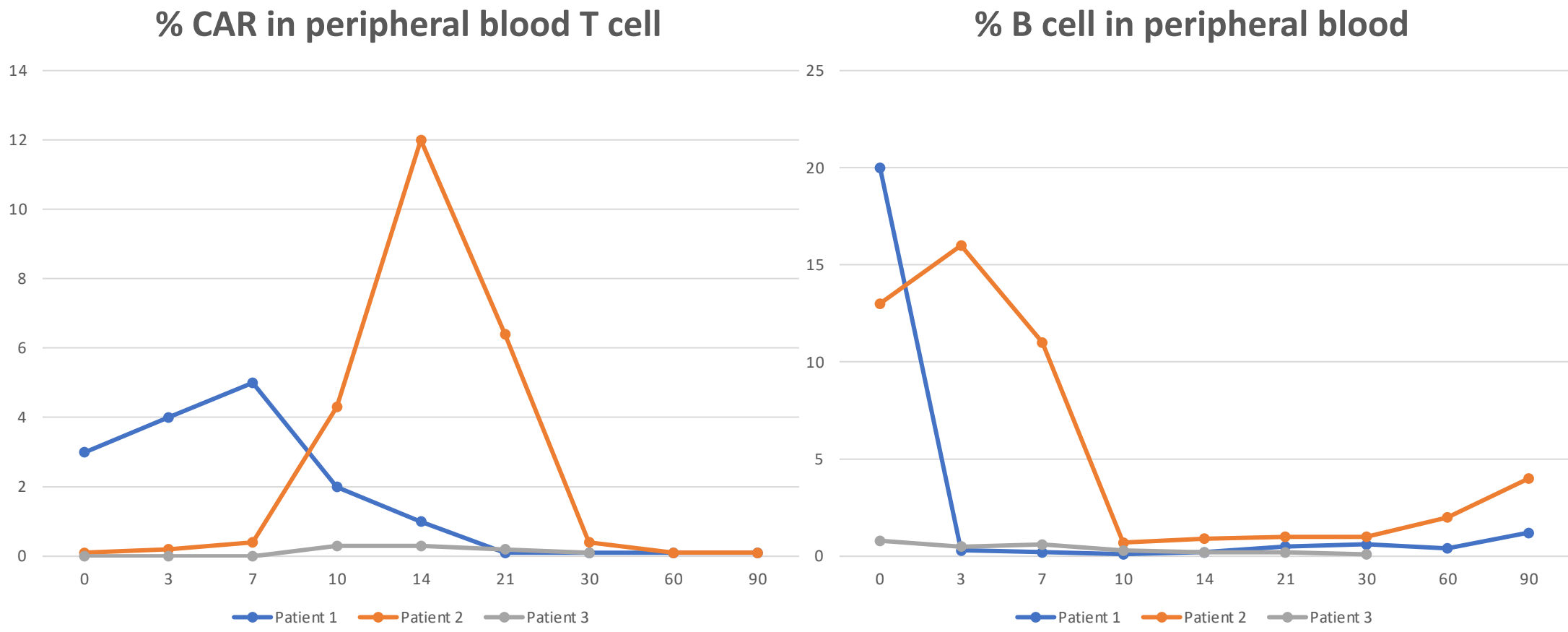
- **Study design**
  - Phase I 3+3 dose escalation study
  - 4 dose level:
    - 0.5 x10e6 cell/kg
    - 1 x10e6 cell/kg
    - 2 x10e6 cell/kg
    - 4 x10e6 cell/kg



Preliminary result from first cohort

Patient ID	Age	Sex	Diagnosis	Disease status	Line of therapy	Status before CAR T infusion	CAR T cell dose (X10e6 cell/kg)
PBCU01	59	male	SLL/CLL	2nd relapse	2	Minimal disease after salvage chemo	0.3
PBCU02	55	female	SLL/CLL	Refractory	4	BM involvement 60% and progressive cervical lymphadenopathy after salvage chemo	0.5
PBCU03	57	female	FL	3nd relpase	3	Minimal disease after salvage chemo	0.5

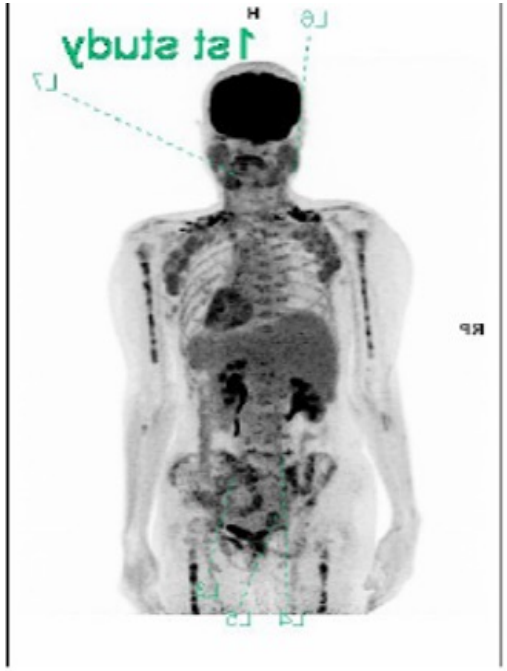
Post PB-CD19 CAR T cell infusion monitoring



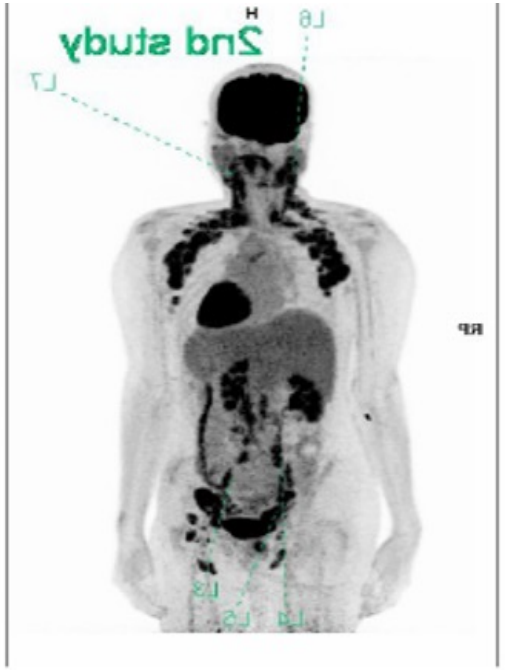
Adverse Events and treatment outcome

Patient ID	CAR T cell dose (X10e6 cell/kg)	Maximum CRS	Maximum ICANS	AEs	Day 30 evaluation	Current status
PBCU01 CLL	0.5	0	0	Grade 3 Heme	CMR	PD at 3 months
	2	0	0	Grade 3 Heme	CR	CR at 2 months
PBCU02 CLL	0.5	1	0	Grade 3 Heme	BM: CR,LN: PMR	PD at 3 months
	2	0	0	Grade 3 Heme	BM:CR, LN: CR	CR at 4 months
PBCU03 Follicular	0.5	0	0	Grade 3 Heme	PMR	PD at 3 months

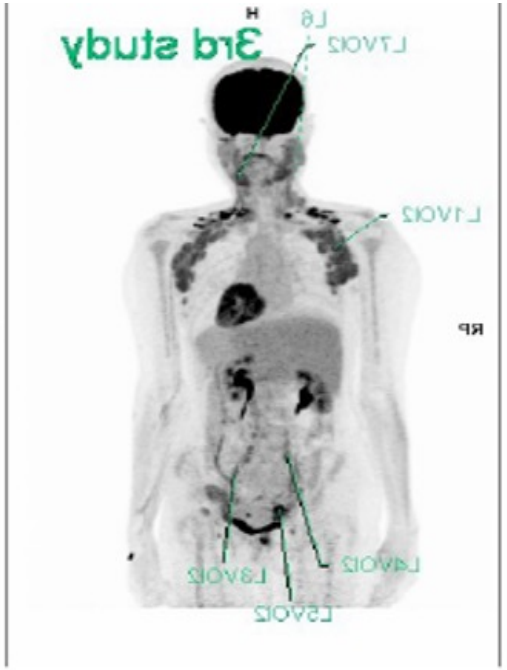
Patient#2: PET-CT before and after CAR T cell



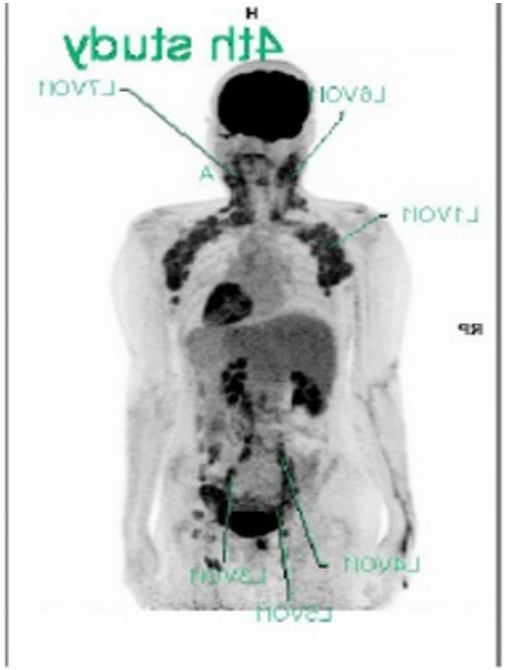
Enroll



Salvage



1st CAR.



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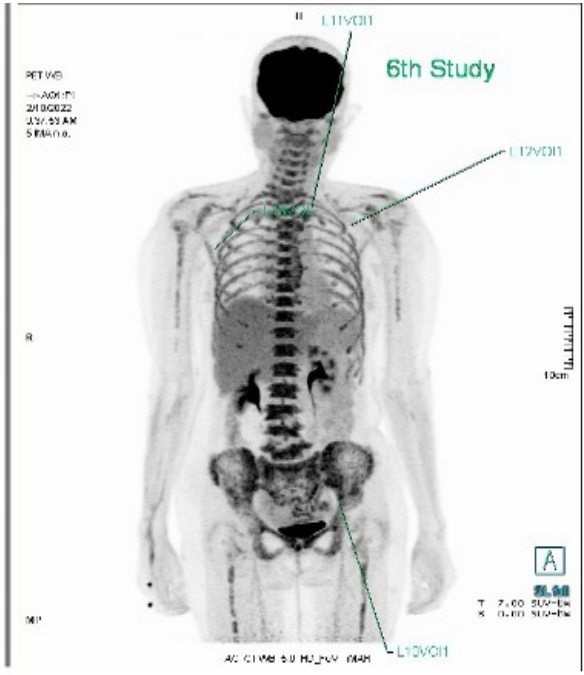


2nd CAR

Clinical trial of PiggyBac CD-19 CAR T cell for ALL and NHL

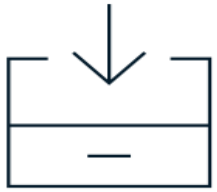
- Phase I/II clinical trial for safety and efficacy evaluation started in 2020
- Established safety profile in first cohort
- Clinical trial will be complete in 2022
- Start in-house service at cost for relapse and refractory leukemia and lymphoma in 2023

(Nagoya U support GMP grade plasmid)

Point-Of-Care Cell Processing Facility

Solutions to accelerate ATMPs development

Potential solutions



Create lower barriers to market access

Implement the following measures to facilitate use of real-world patient data to demonstrate long-term safety and efficacy:

- Analyze patient data while assuring patient privacy through technological developments.[1]
- Allow hospitals to act as data analysis centers that share insights from their data but not the actual data.

Increase investments

Government support of biotech ecosystems would build on Europe's current strengths in CGTs.

Encourage closer collaboration

Facilitate collaboration between key stakeholders:

- Payers and biopharmaceutical companies could establish new, more affordable pricing mechanisms.
- Hospitals and manufacturers could automate manufacturing and bring it closer to the point of care.

[1]For instance, distributed ledgering and machine learning.

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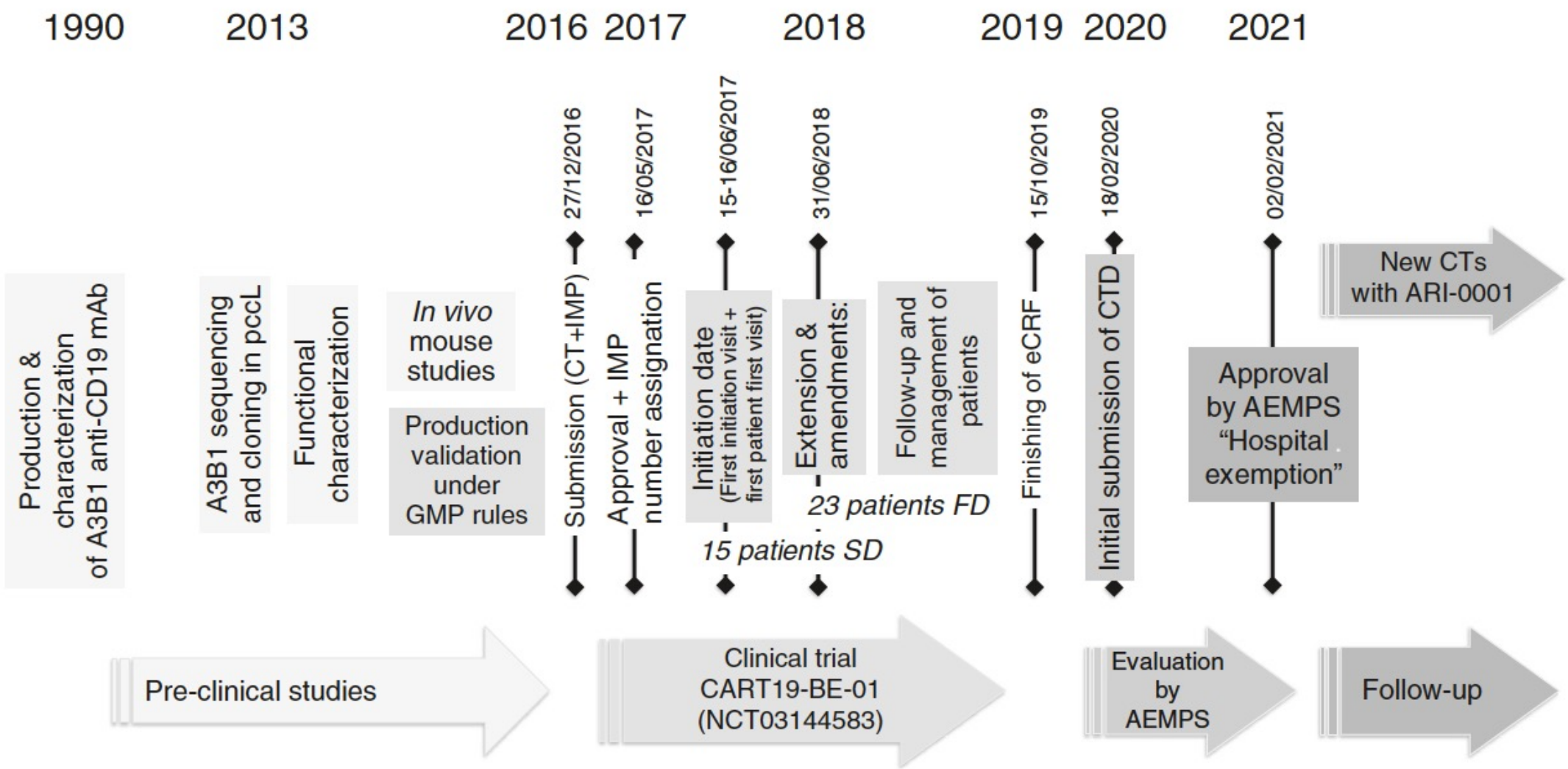
Point of Care based CAR-T cell approval in Europe



Cell and Gene Therapy Manufacturing Center

Approved layout by Thai FDA: FEB 2018

Approved facility by Thai FDA: APR 2021

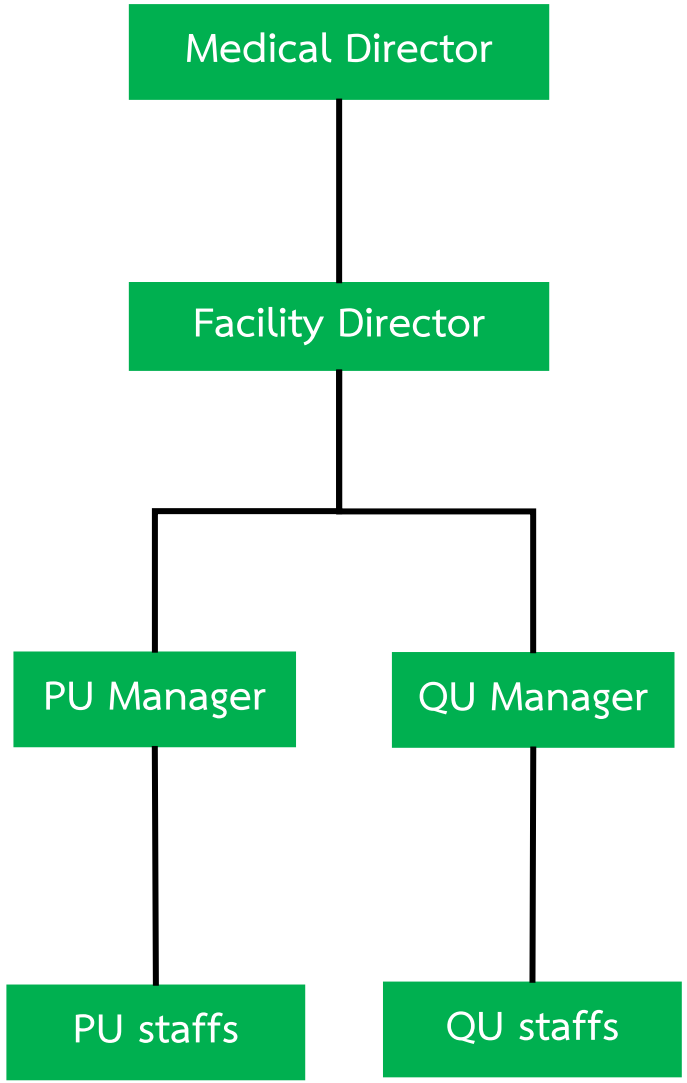
Facility development

- Approved layout by Thai FDA:FEB 2018
- Facility renovate: 2018 -2021
- Approved facility by Thai FDA: JUN 2021
- Qualification completed: DEC 2021
- Start manufacturing: JAN 2022
- Set up PQS follow PIC/S GMP

Cell and Gene Therapy Manufacturing Center

- First Thai FDA-GMP approve Institutional based Facility
- 200 SQM facility with 1 Grade-B and 3 Grade-C processing suite
- Comprehesive processing platform: Isolation, Selection, Editing, Expasion, Collection and Cryopreservation
- Product
  - Stem cells: IPSCs, HSCTs, Cornea SCs
  - Immune cells: CAR-T cells, CAR-NK cells, CTLs
- Role:
  - Process GMP compliance product for phase I/II clinical trial and in-house service
  - Process Development, SOP development, in-process control and final product release
  - IND preparation

GMP-compliance cell processing



Product pipeline

Product	2565	2566	2567	2568	2569
CD-19 CAR T cell (ALL/DLBCL)	Clinical trial	Service			
BCMA CAR T cell (Multiple Myeloma)	Preclinical study	Clinical trial		Service	
CD-117 CAR T cell (AML)	Preclinical study		Clinical trial		Service
Graft manipulation (Haploidentical HSCT)	Service				
Viral Specific-CTL (Infection post HSCT)	Service				

Support needed from government agency

- **Funding for early phase clinical trial** (matching by institue rather than private sector)
  - Increase patient access to effective therapy through clinical trial
  - Increase opportunity to further develop into commercial product
  - Develop competent patient care team
- **Funding for set up and maintain quality system**
  - Consultation from local and international expert
  - Hiring and training to get competent personnel in production unit and quality unit
- **Regulatory support** for instituional based processing facility

Acknowledgement

- Cancer Immunotherapy Excellence Center
- Cellular Immunotherapy Research Unit
- Excellence Center for Stem Cell and Cell Therapy
- Excellence Center for Comprehensive Cancer
- Center for Hematopoietic Stem cell Transplatation and Cell therapy
- Collaborators:

Question?

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