Adoptive Cell Therapy with Gene-modified T cells

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COI Disclosure Information

Hiroshi SHIKU

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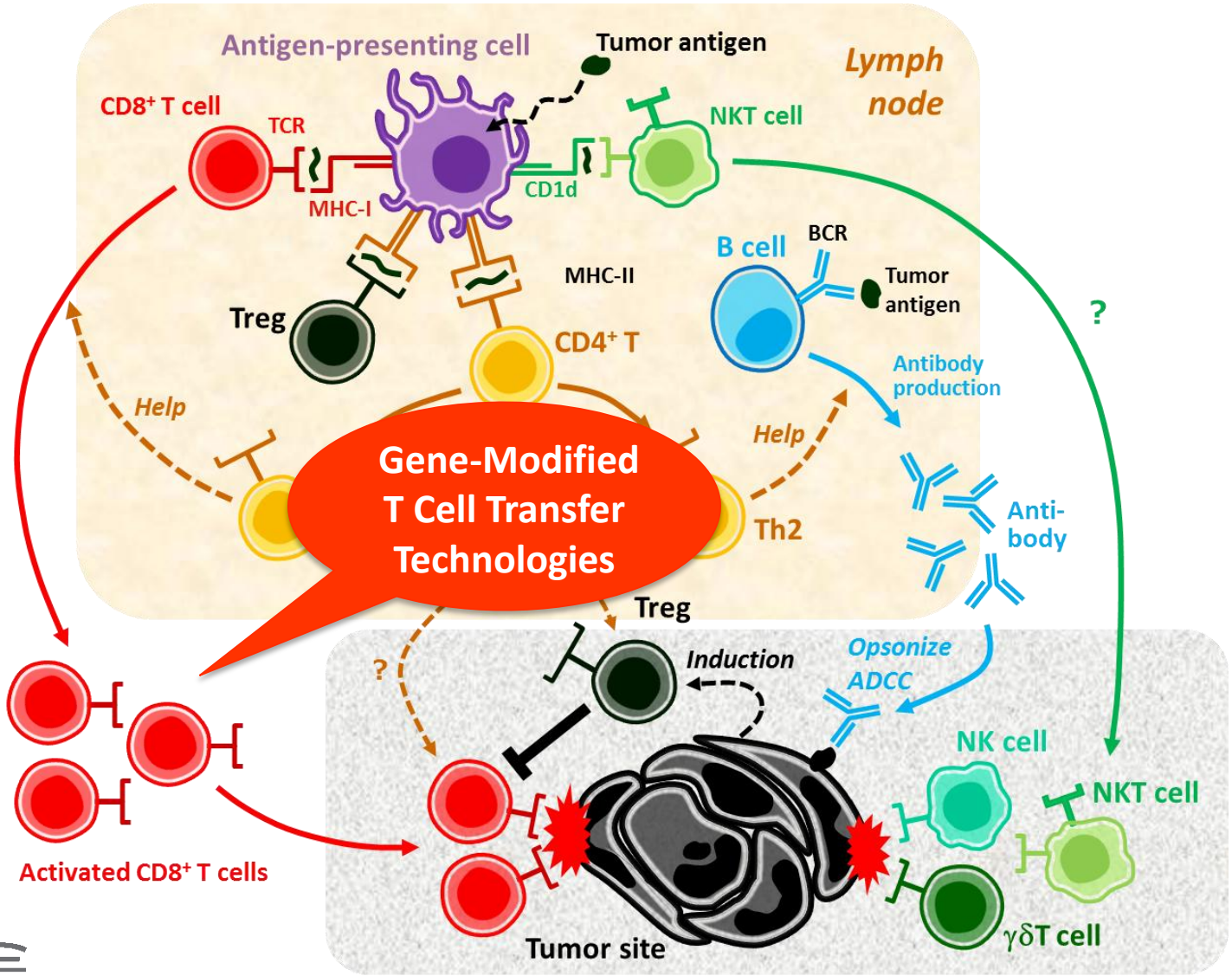
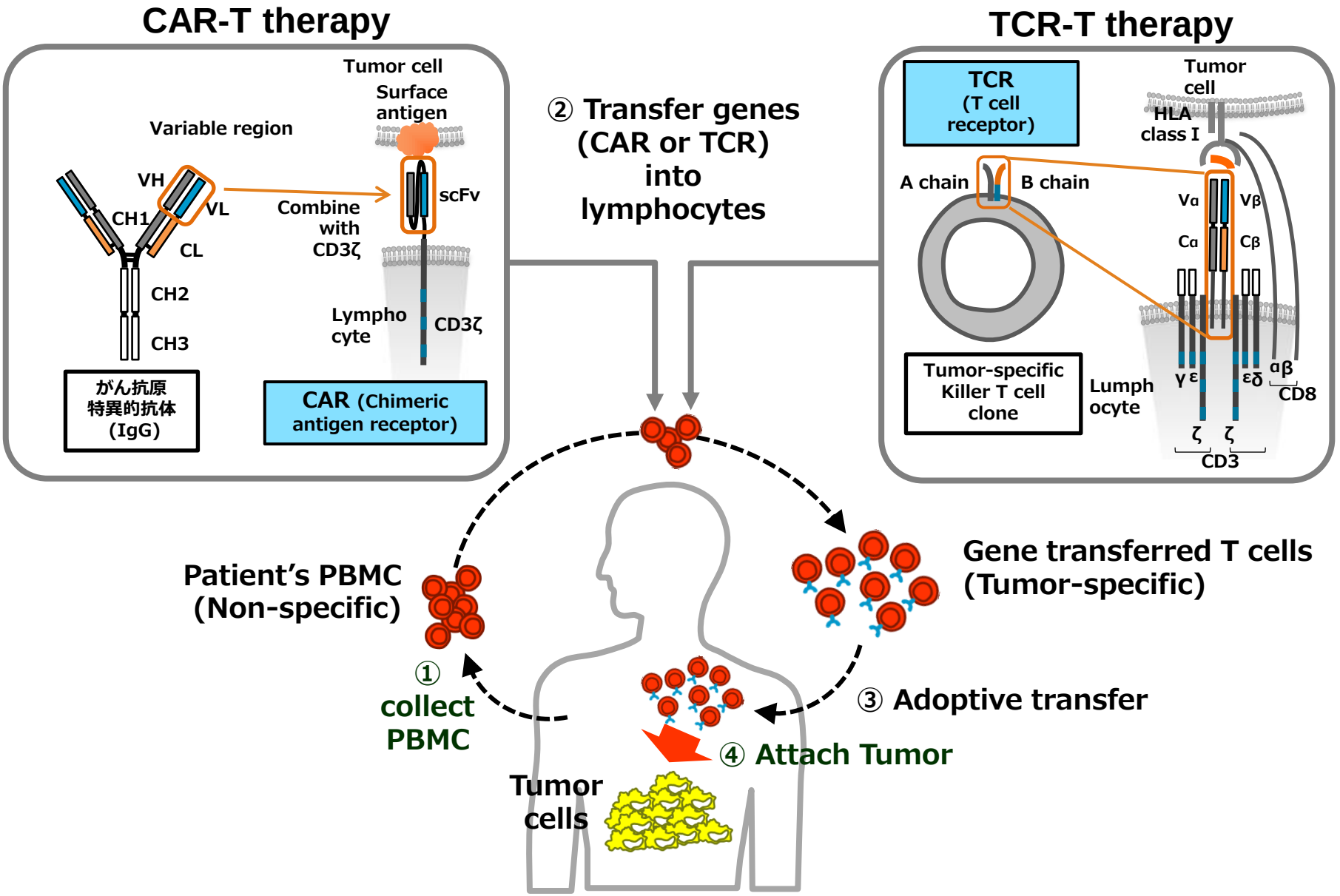
A Variety of Approaches in Cancer Immunotherapy -Adoptive Cell Therapy-



CAR／TCR gene transfer T cell therapy

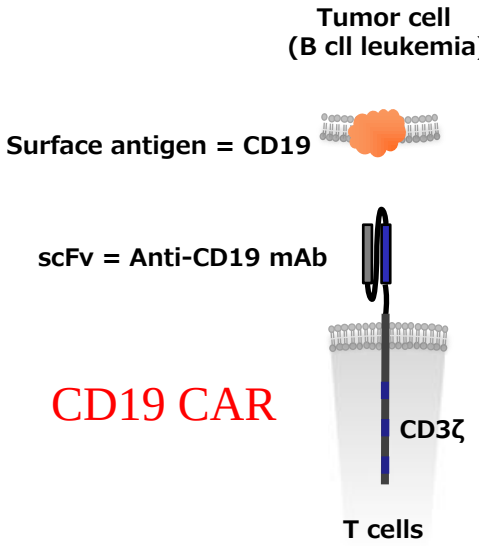


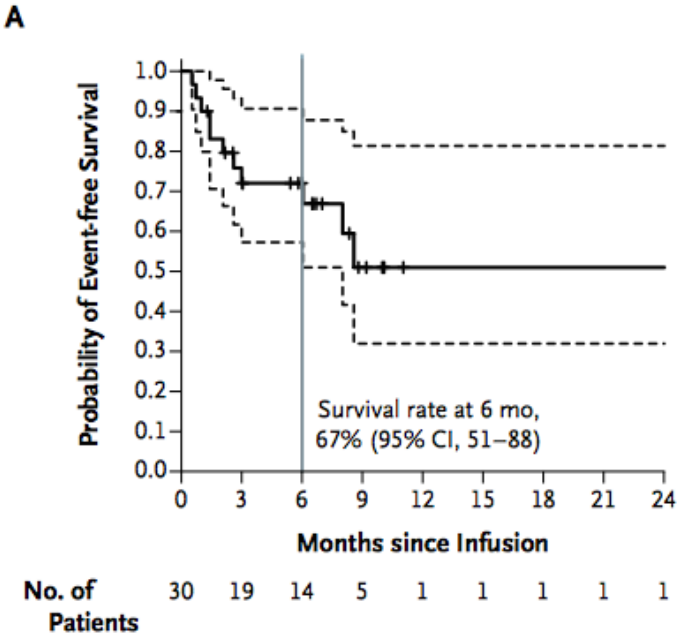
The NEW ENGLAND JOURNAL of MEDICINE

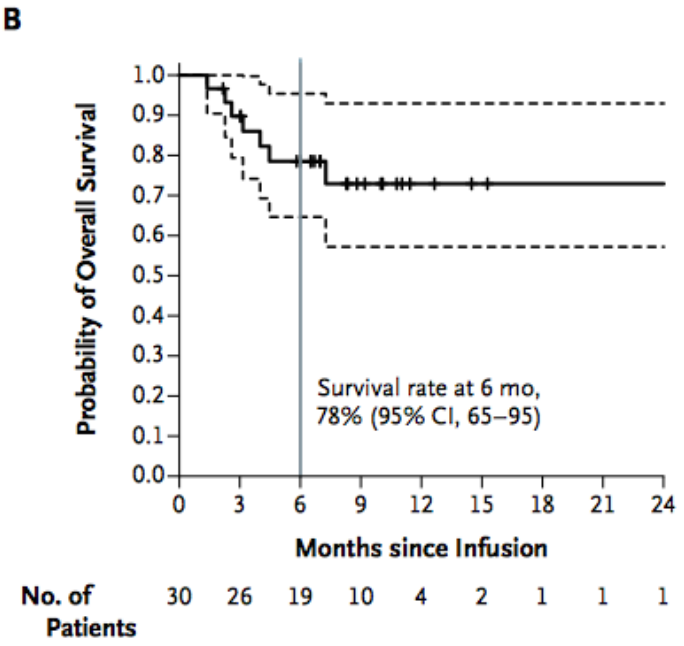
ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Pt with relapsed or refractory ALL: 30Pt.
CR:90%
6 month Event-free survival: 67%
6 month Overall survival: 78%

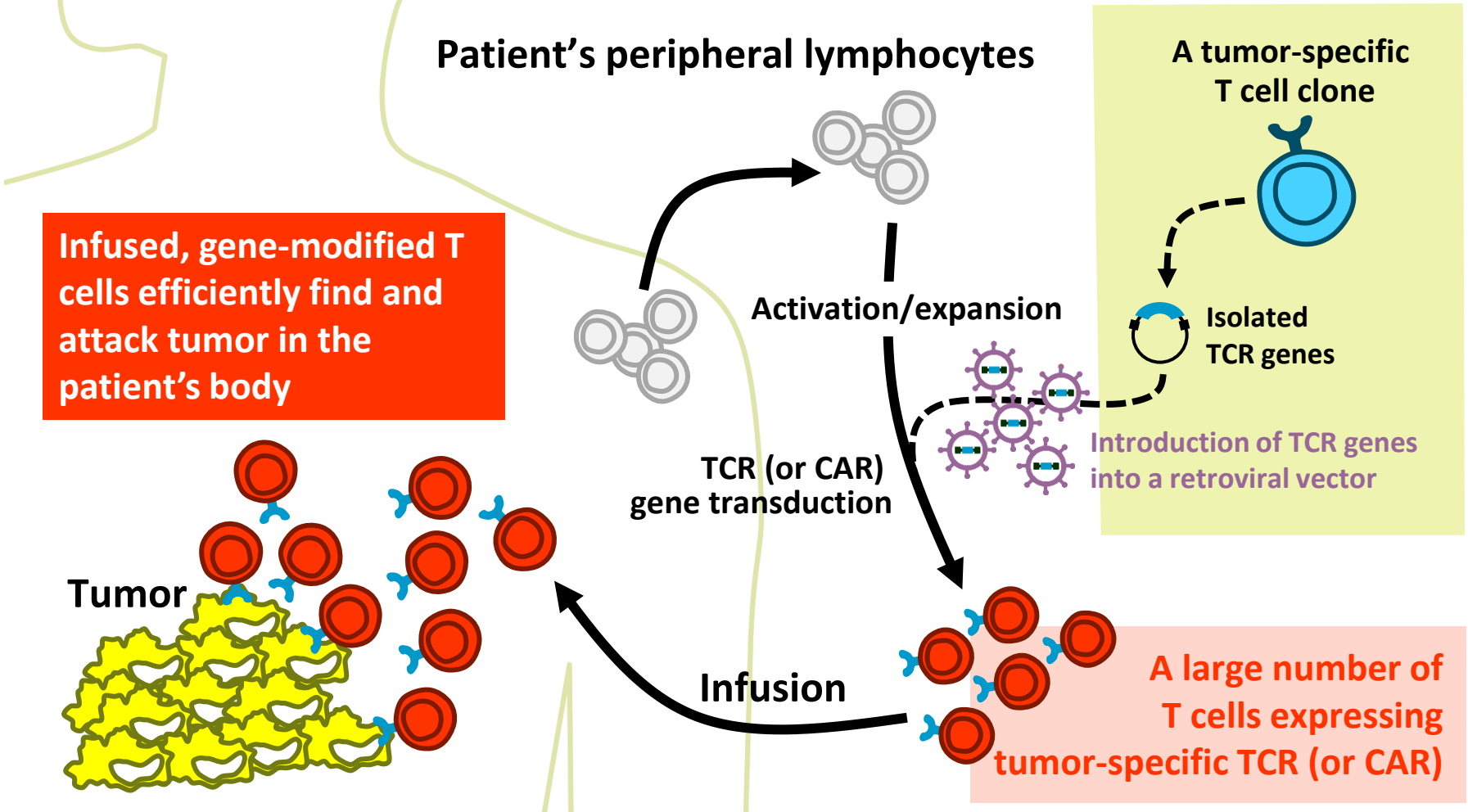






Maude et al. NEJM 2014

Adoptive T Cell Transfer Using TCR or CAR Gene-Transduced T Cells



MIE UNIVERSITY

Today's Topics

Adoptive Cell Therapy with TCR Engineered T Cells

CAR-T cells for Peptide/MHC complex:

A New Approach of Adoptive Cell Therapy ?

Today's Topics

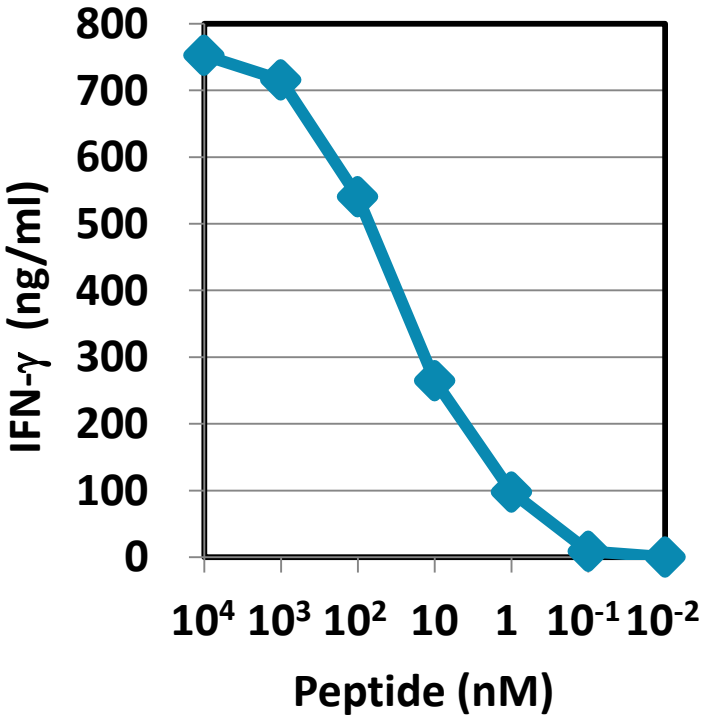
Adoptive Cell Therapy with TCR Engineered T Cells

CAR-T cells for Peptide/MHC complex:

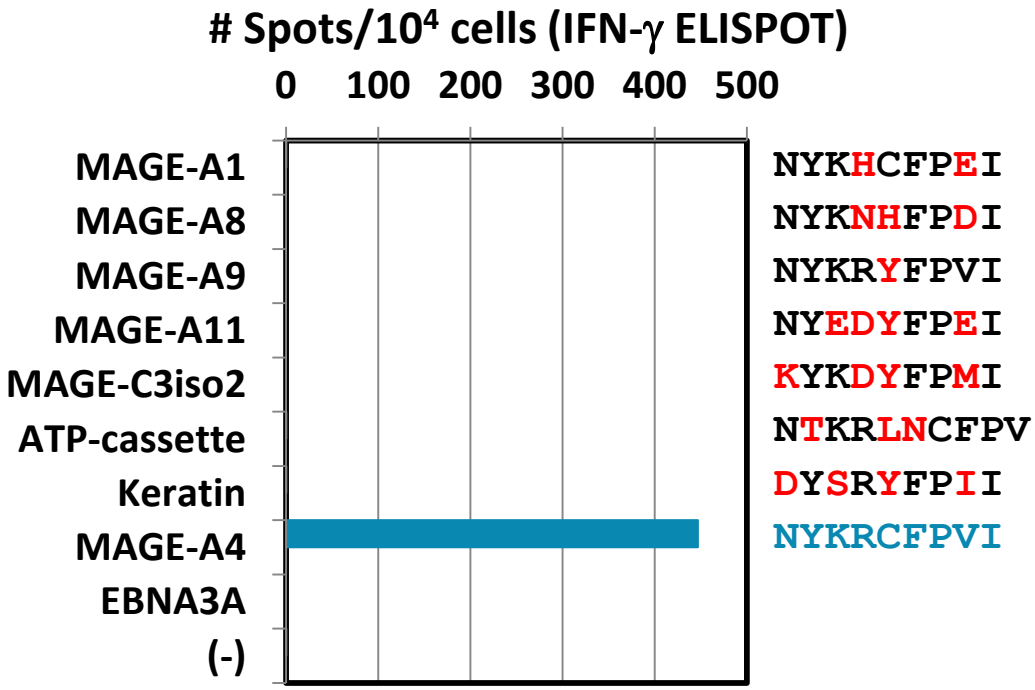
A New Approach of Adoptive Cell Therapy ?

A Human CTL Clone #2-28 Specifically Recognizes a MAGE-A4 Antigen-Derived Epitope Peptide in a HLA-A2402-Restricted Manner

Recognition of MAGE-A4$_{143-151}$ epitope peptide (NYKRCFPVI) by CTL clone #2-28 in vitro



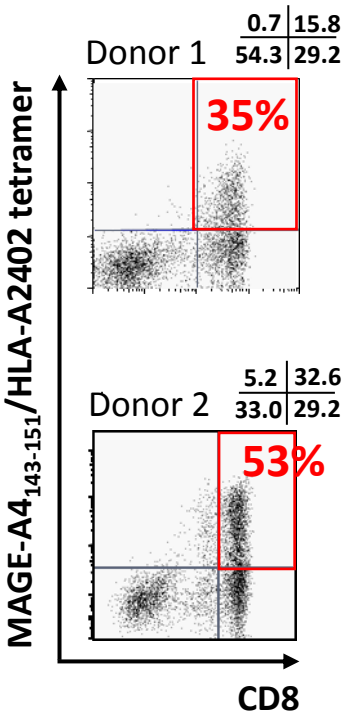
Specificity of antigen recognition by CTL clone #2-28 in vitro



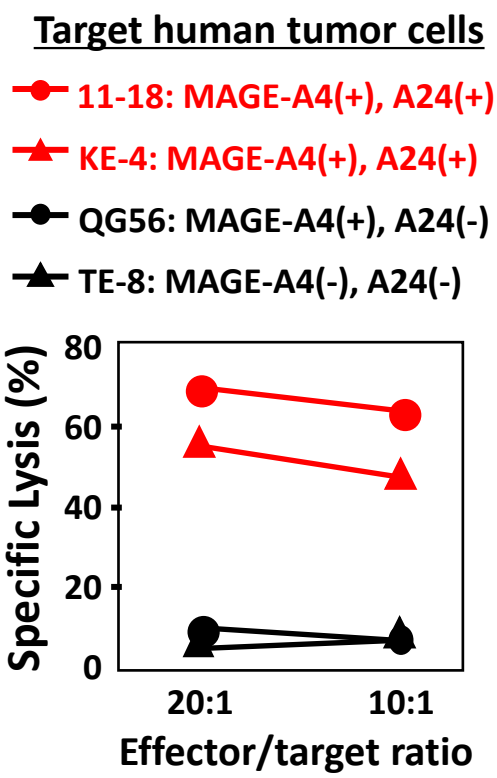
Miyahara et al. Clin Cancer Res 2005

TCR Gene-Engineered CD8+ T Cells Become Reactive with Target Antigen-Expressing Tumor Cells

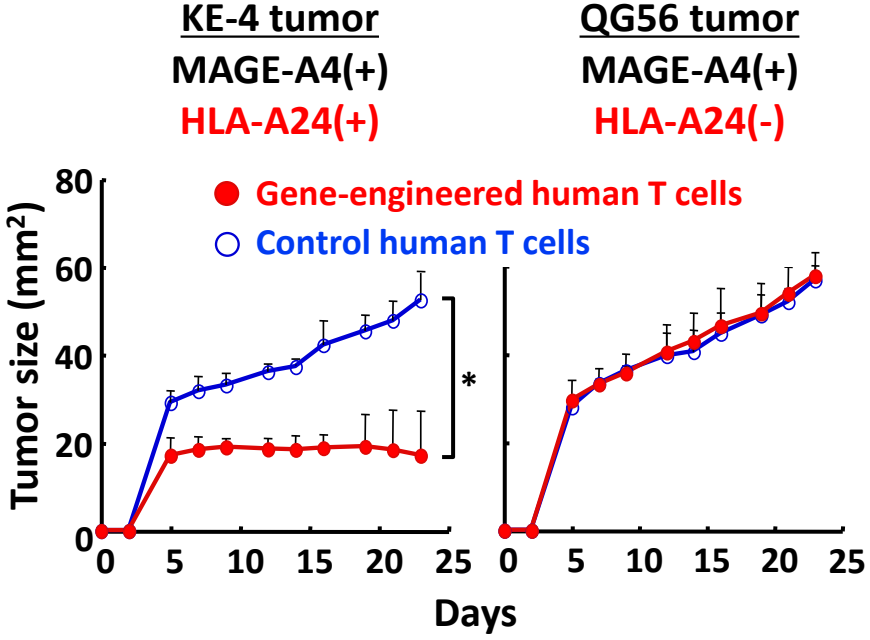
Efficient expression



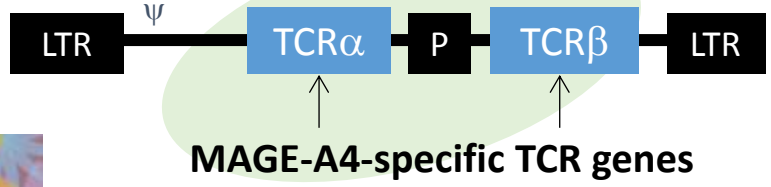
Specific cytotoxicity



In vivo efficacy (mouse xenograft model)

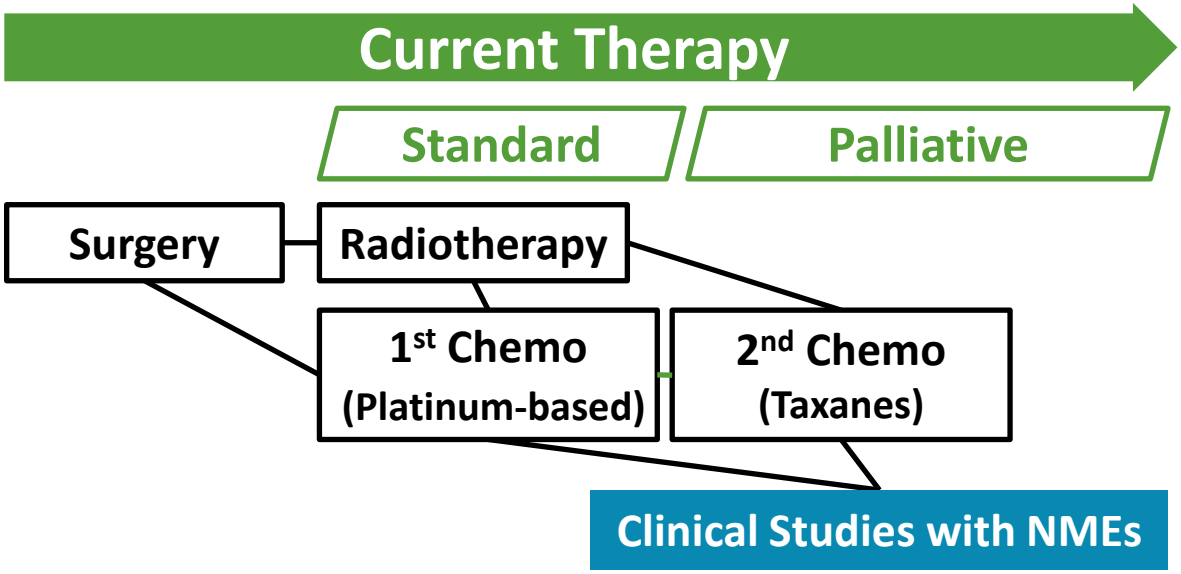


Retroviral TCR Vector



Shirakura et al. Cancer Sci 2012

Unmet Medical Need for Recurrent/Metastatic Esophageal Cancer

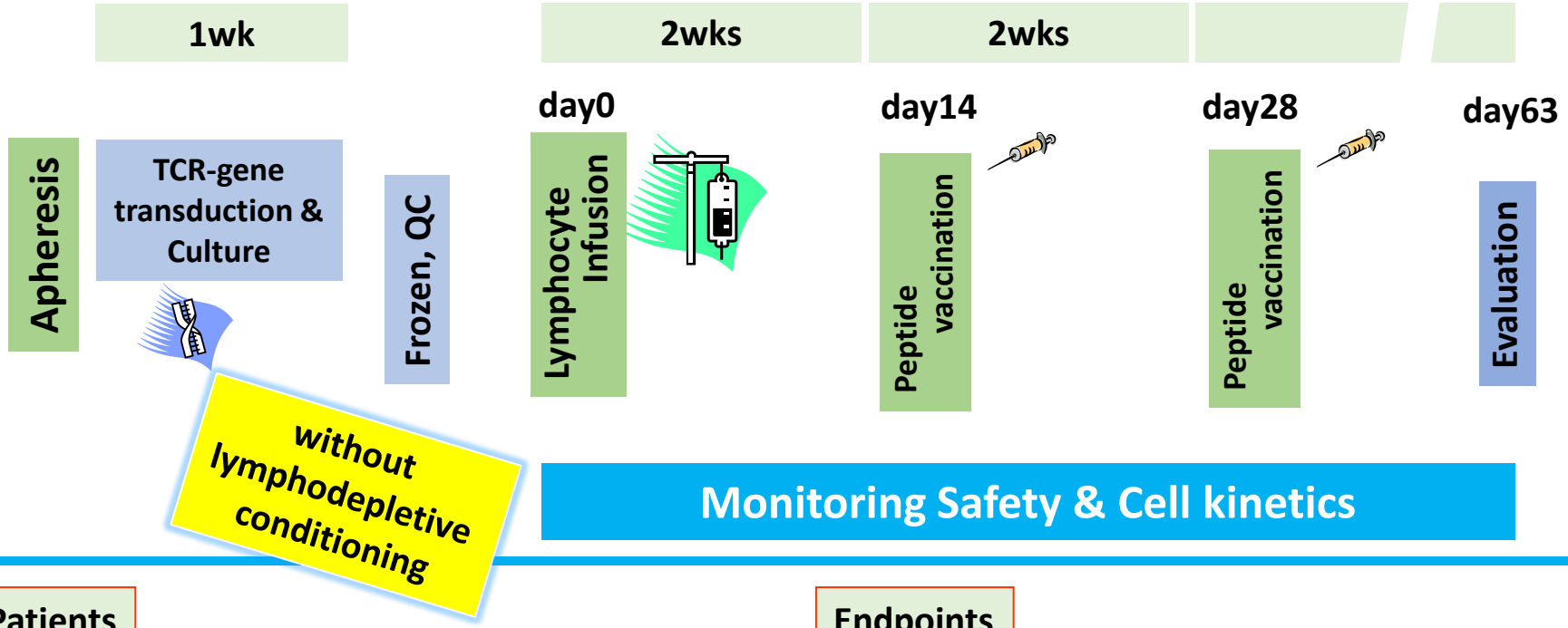


- 50% survival in recurrent/ metastatic esophageal cancer, refractory to platinum-based regimen (standard therapy), is approximately 6 months.
- No other approved options available but Taxanes.

1. Less options of effective modalities.
2. Far behind compared with colorectal cancer or gastric cancer.
3. Squamous cell carcinoma is major in Asia, while adenocarcinoma in US and Europe

Necessity of (Asian-oriented) effective esophageal cancer therapy

First-in-man trial of adoptive transfer of lymphocytes transduced with MAGE-A4-specific TCR gene for patients with esophageal cancer



Patients

MAGE-A4 expression(+) HLA-A*24:02(+)
Esophageal cancer

Cell-dose escalating study

$2x10^8$ cells infusion for 3 pts
$1x10^9$ cells infusion for 3 pts
$5x10^9$ cells infusion for 3 pts

Endpoints

- **Primary**
  - Safety
  - Adverse events
  - RCR(replication competent retrovirus)
  - Cell clonality by LAM-PCR
- **Secondary**
  - Cell kinetics, Tissue infiltration
  - Immune reaction, Tumor response

Patients' Characteristics and Adverse Events after TCR Gene-Engineered Lymphocytes Transfer

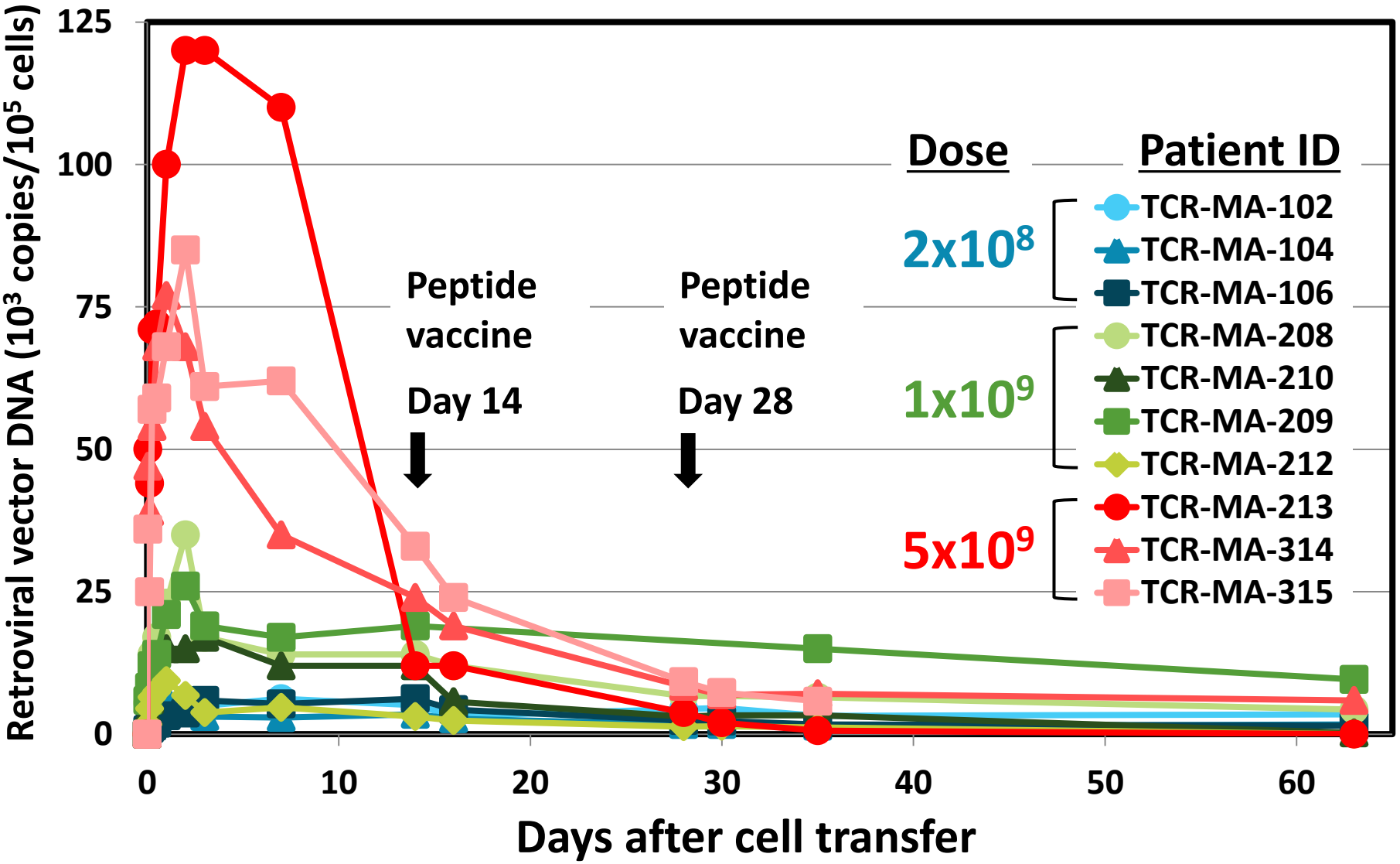
Cohort	Cell doses allocated	Patient ID	Age/sex	MAGE-A4 expressions		Tumor lesions	Number of IFN-γ+ CD8 T cell infused	Adverse events (grade)
				PCR*	IHC**/57B			
1	$2x10^8$	TCR-MA-102	68/M	2,880	NA	liver	$1.46x10^7$	none
	$2x10^8$	TCR-MA-104	56/M	4,847	20%(++)	esophagus	$1.24x10^7$	none
	$2x10^8$	TCR-MA-106	73/M	2,215	10%(+)	esophagus, lymph node	$1.48x10^7$	skin reaction(I)***
2	$1x10^9$	TCR-MA-208	67/M	7,942	30%(+)	lymph node	$6.8x10^7$	none
	$1x10^9$	TCR-MA-209	57/M	1,352	70%(++ or +++)	lymph node	$1.3x10^8$	none
	$1x10^9$	TCR-MA-210	54/M	312	30%(+++)	esophagus, lung, lymph node	$9.6x10^7$	skin reaction(I)***
	$1x10^9$	TCR-MA-212	43/M	1,765	20%(+)	lymph node	$2.6x10^8$	skin reaction(I)***
3	$5x10^9$	TCR-MA-213	68/M	749	NA	lymph node	$5.3x10^8$	none
	$5x10^9$	TCR-MA-314	64/M	82	<5%(+)	lymph node	$6.6x10^8$	none
	$5x10^9$	TCR-MA-315	57/F	NA	20%(++)	lung, lymph node	$9.75x10^8$	skin reaction(I)***

* copies numbers amlified by RealTime PCR.

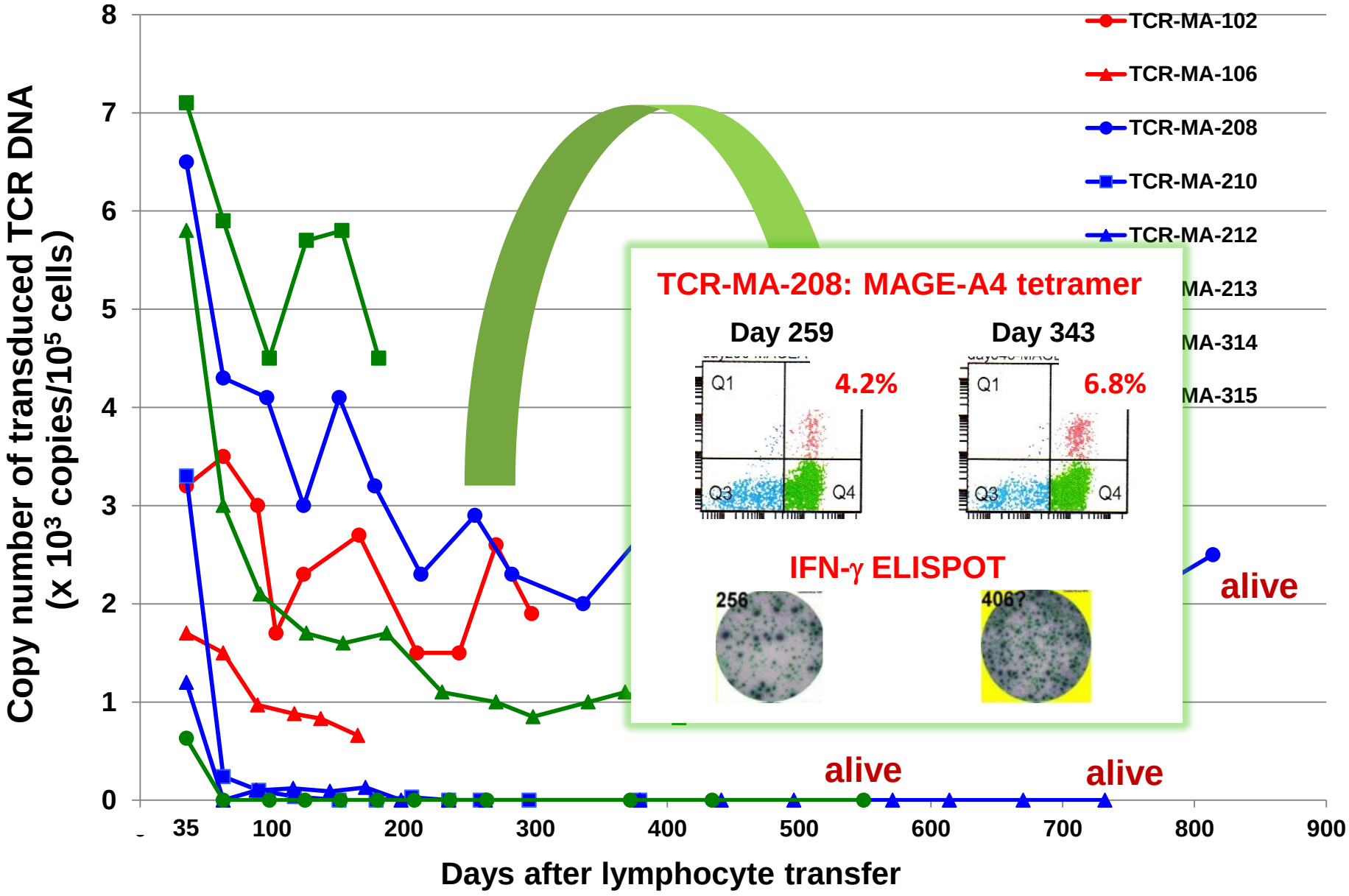
** positive percentage and intensity of immunohistochemical staining.

*** skin reactions were related to peptide vaccinations.

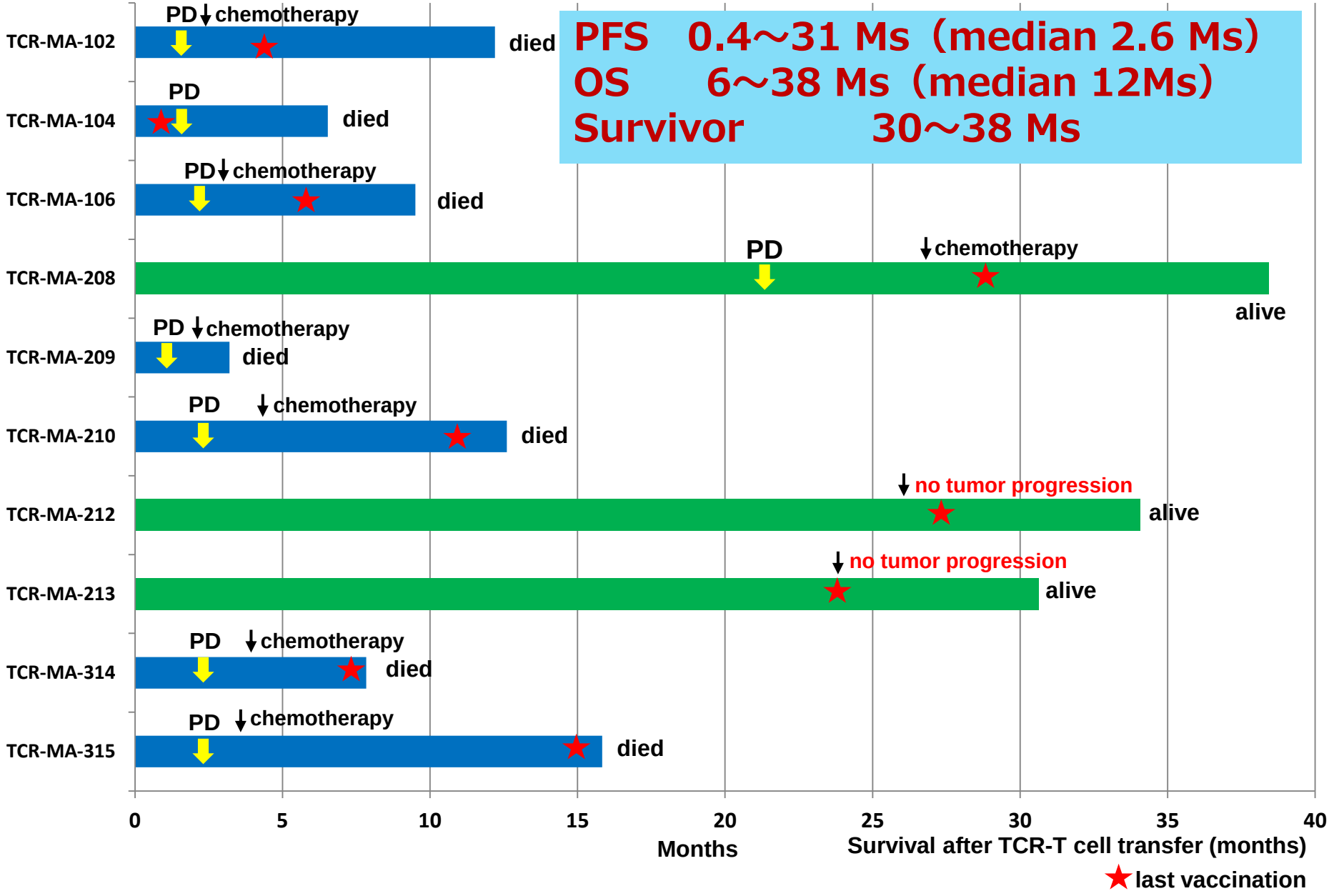
Pharmacokinetics of Transferred TCR Gene-Engineered Lymphocytes in the Peripheral Blood



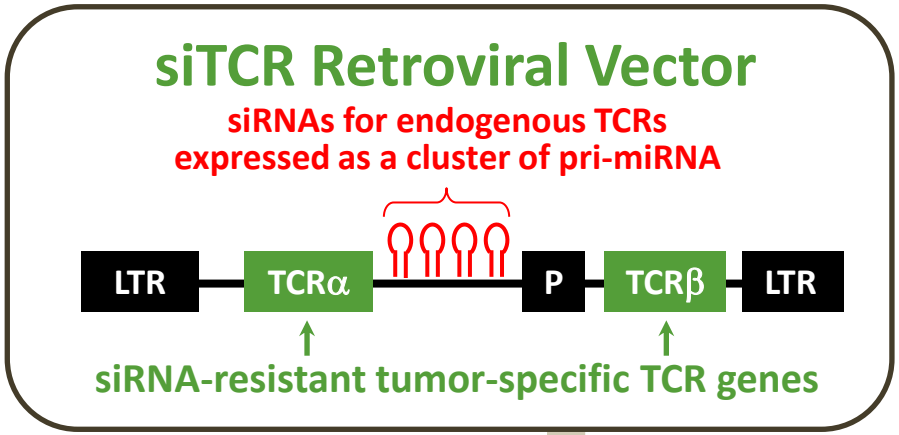
Long Term Persistence of TCR Gene-Transduced Cells in the Peripheral Blood of 5 Patients



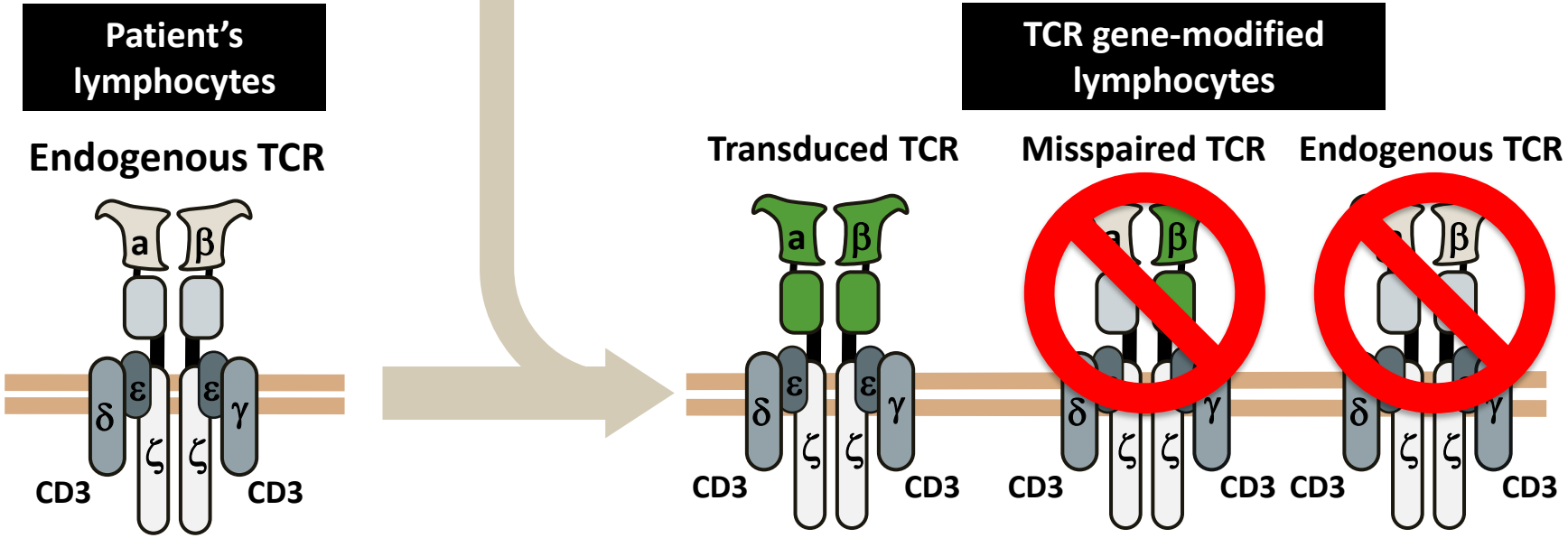
Clinical course of 10 enrolled patients



Novel retrovirus vector that reduce the expression of endogenous TCR ~siTCR vector~



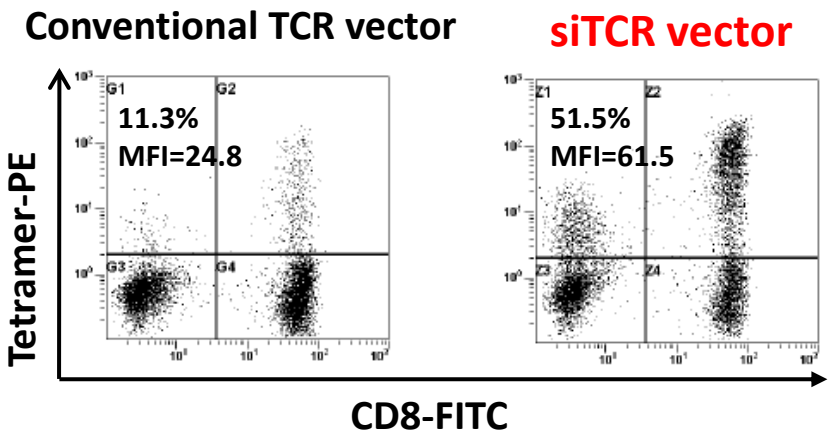
- ✧ ***Enhanced expression of transduced tumor-specific TCR***
- ✧ ***Inhibition of creation of self-reactive TCR***

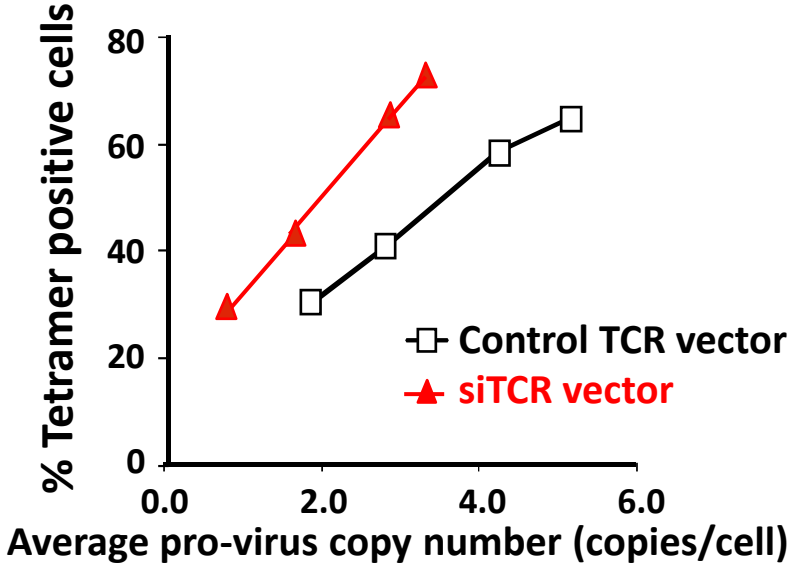


Okamoto et al. Cancer Res 2009

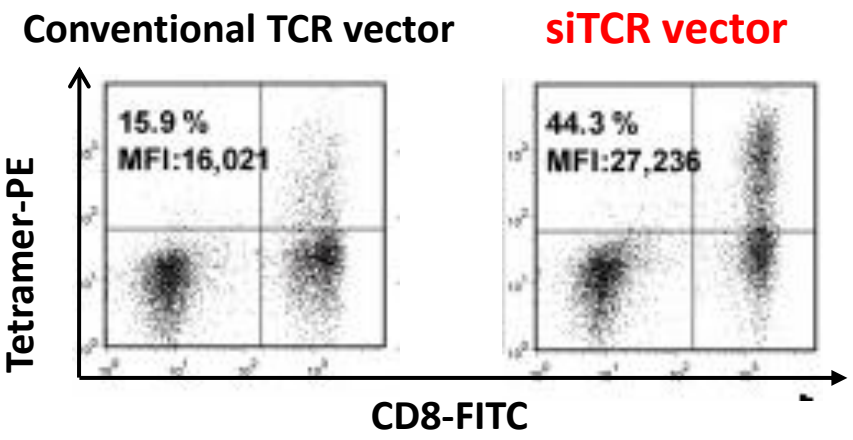
Suppression of Endogenous TCR Results in Higher Expression of Transduced MAGE-A4- or WT1-Specific TCR

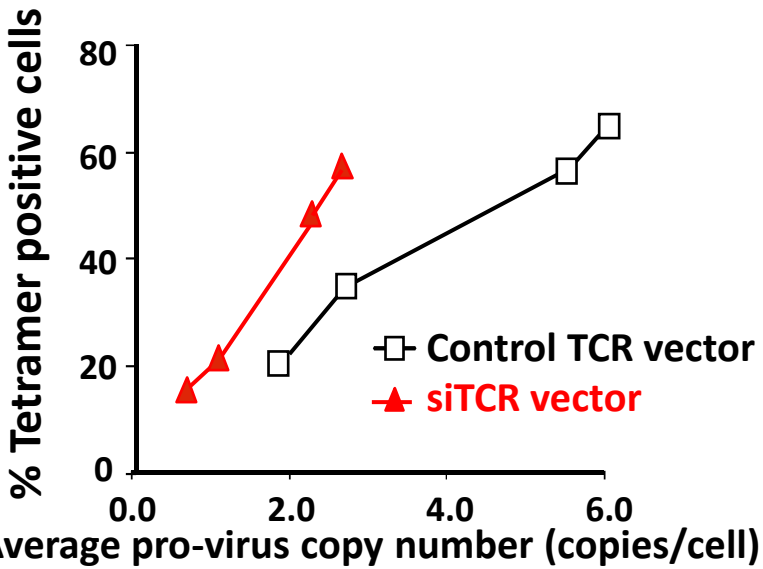
MAGE-A4-specific TCR





WT1-specific TCR





Multi-institutional Clinical Trials of Adoptive Cell Therapy ongoing

➢ MAGE-A4 TCR (wild type)

Miyahara et al. Clin Cancer Res 2005

- Targets: Solid tumors (esophageal ca, H&N ca, melanoma, etc.)
- Vector: siTCR vector
- Preconditioning: cyclophosph, fludarabine
- **Status: 3 patients administrated**

➢ WT1 TCR (wild type)

Ohminami et al. Blood 2000

- Targets: AML, MDS
- Vector: siTCR vector
- No Preconditioning
- **Status: 6 patients administrated**

➢ NY-ESO-1 TCR (manipulated for high affinity)

Schmid et al. J Immunol 2010

- Targets: Solid tumors (esophageal ca, H&N ca, melanoma, etc.)
- Vector: siTCR vector
- Preconditioning: cyclophosphamide, fludarabine
- **Status: 3 patients administrated**

Today's Topics

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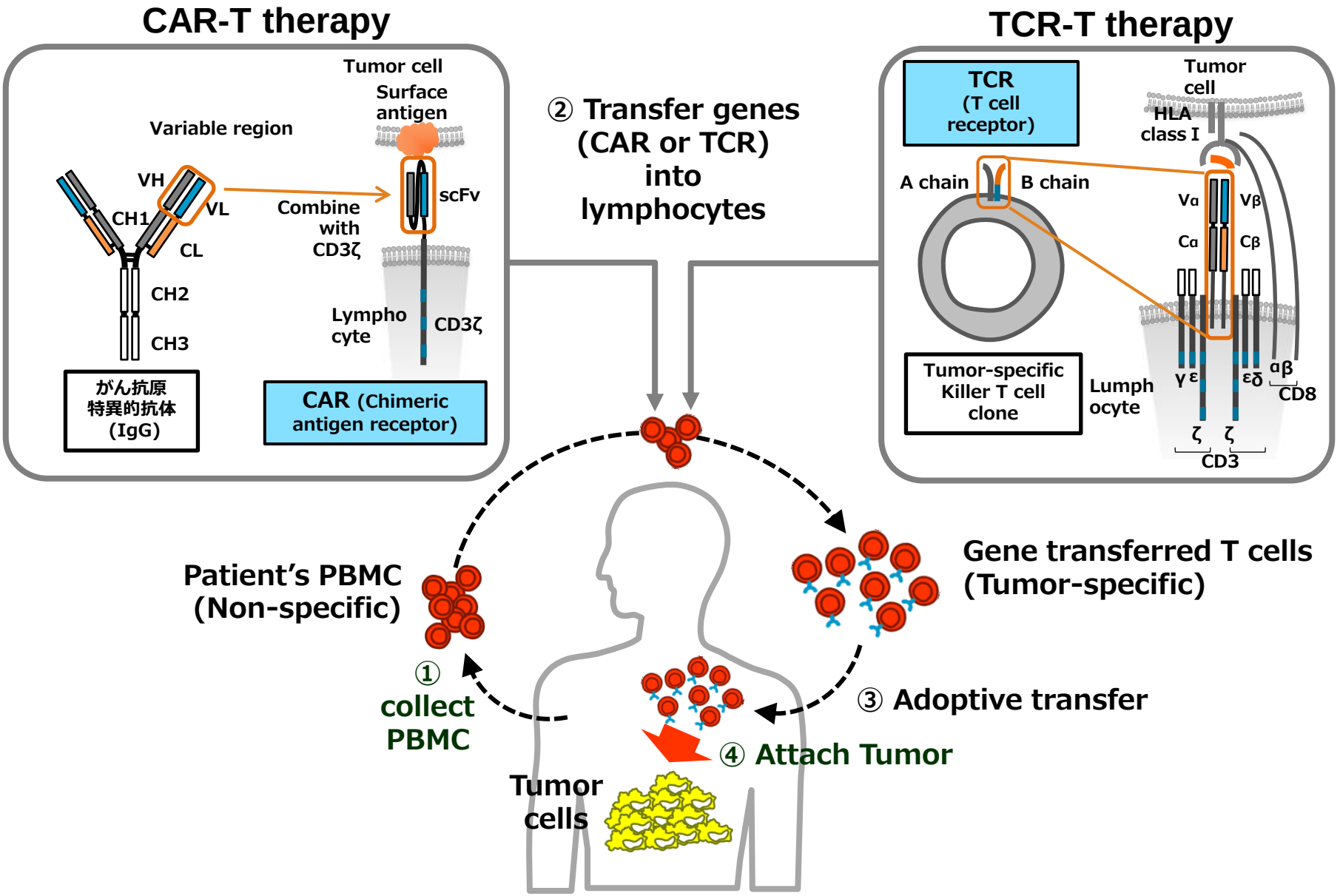
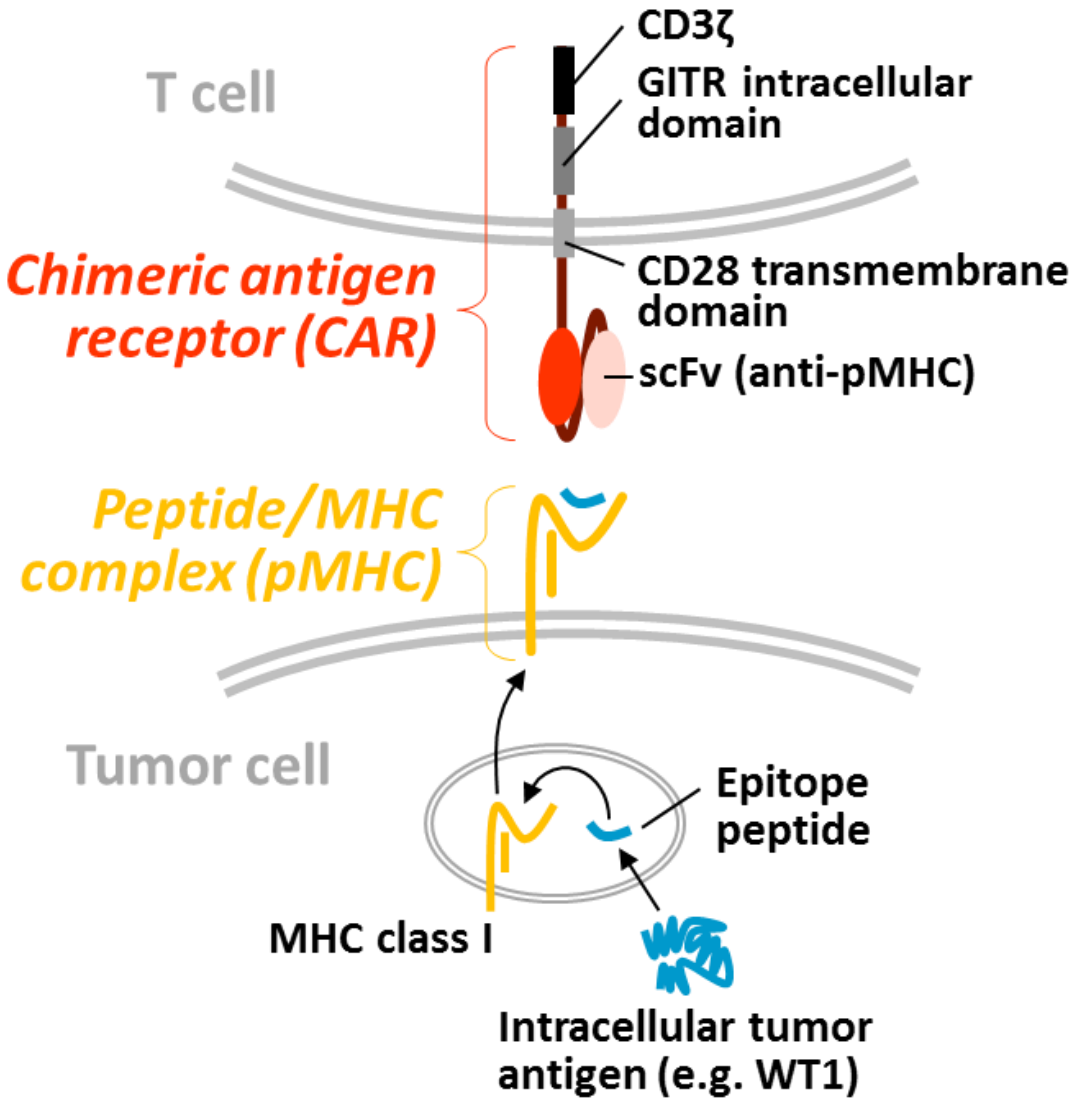
CAR-T cells for Peptide/MHC complex:

A New Approach of Adoptive Cell Therapy ?

CAR／TCR gene transfer T cell therapy



Chimeric Antigen Receptor(CAR)
that recognizes intracellular antigens



Anti-CD19 CAR therapy is successful.

What is next target?

Our approach:
Develop CARs that recognize cell surface peptide/MHC complex derived from intracellular tumor antigens.

Investigators

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