Adoptive Cellular Therapy
SITC Primer
October 2012

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Gangnam Style


GRATEFUL DEAD
BUILT TO LAST

T-cell therapy at the threshold

Carl June, Steven A Rosenberg, Michel Sadelain & Jeffrey S Weber

Despite impressive clinical activity in B-cell lymphoma and melanoma, questions remain about the immunobiology of adoptive T-cell therapies.

Adoptive T-cell therapy in advanced metastatic melanoma or B-cell leukemias is garnering increasingly encouraging clinical data. *Nature Biotechnology* approached several experts in the field to seek their insights into some of the challenges of optimizing and commercializing these experimental treatments.

What factors in the host and tumor microenvironment might compromise T-cell therapy?

Michel Sadelain: The tumor microenvironment is the battlefield where immune effectors either eradicate a tumor or fail, succumbing to various inhibitory mechanisms promoted by the tumor. The sources of such inhibition are multiple, including regulatory T cells, type 2 macrophages, myeloid suppressor cells and the tumor cells themselves. The players are multiple and differ between tumor types and individuals. Although it is not a black box anymore, a lot remains to be learned. Extratumoral factors affect adoptive T-cell therapy in many ways. Examples include medullary or splenic reservoirs of myeloid suppressor cells; dysfunctional dendritic cells in lymph nodes; and extratumoral expression of antigen or cross-reactive peptides, which are the cause of 'on-target, off-tumor' side effects.

Michel Sadelain is Director, Center for Cell Engineering & Gene Transfer and Gene Expression Laboratory, and Stephen and Barbara Friedman Chair, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York.

Carl June is in the Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; Steven A. Rosenberg is in the Surgery Branch, National Cancer Institute, US National Institutes of Health, Bethesda, Maryland, USA; Michael Sadelain is at the Center for Cell Engineering, Memorial Sloan-Kettering Cancer Center, New York, New York, USA; and Jeffrey S. Weber is at the Donald A. Adam Comprehensive Melanoma Research Center at H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida, USA.

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Steven A. Rosenberg: There clearly are aspects of the immune system that can regulate if not suppress immune reactions, and dealing with them is important for immunotherapy. In fact, with adoptive T-cell transfer therapy, the critical aspect of getting it to work is first lymphodepleting the patient before we return to the patient either natural antitumor cells or gene-modified antitumor cells. This prior lymphodepletion, using chemotherapy and sometimes with whole body irradiation, eliminates T-regulatory cells, myeloid-derived suppressor cells and other suppressive influences, and that's what can lead to complete durable regression in patients with melanoma who receive cell transfers. So dealing with the tumor microenvironment is critical.

Steven A. Rosenberg is Chief of Surgery at the US National Cancer Institute, Bethesda, MD.

Carl June: Our data show that replicative capacity of the transferred T cells may be a key factor that is required for efficacy of the procedure.

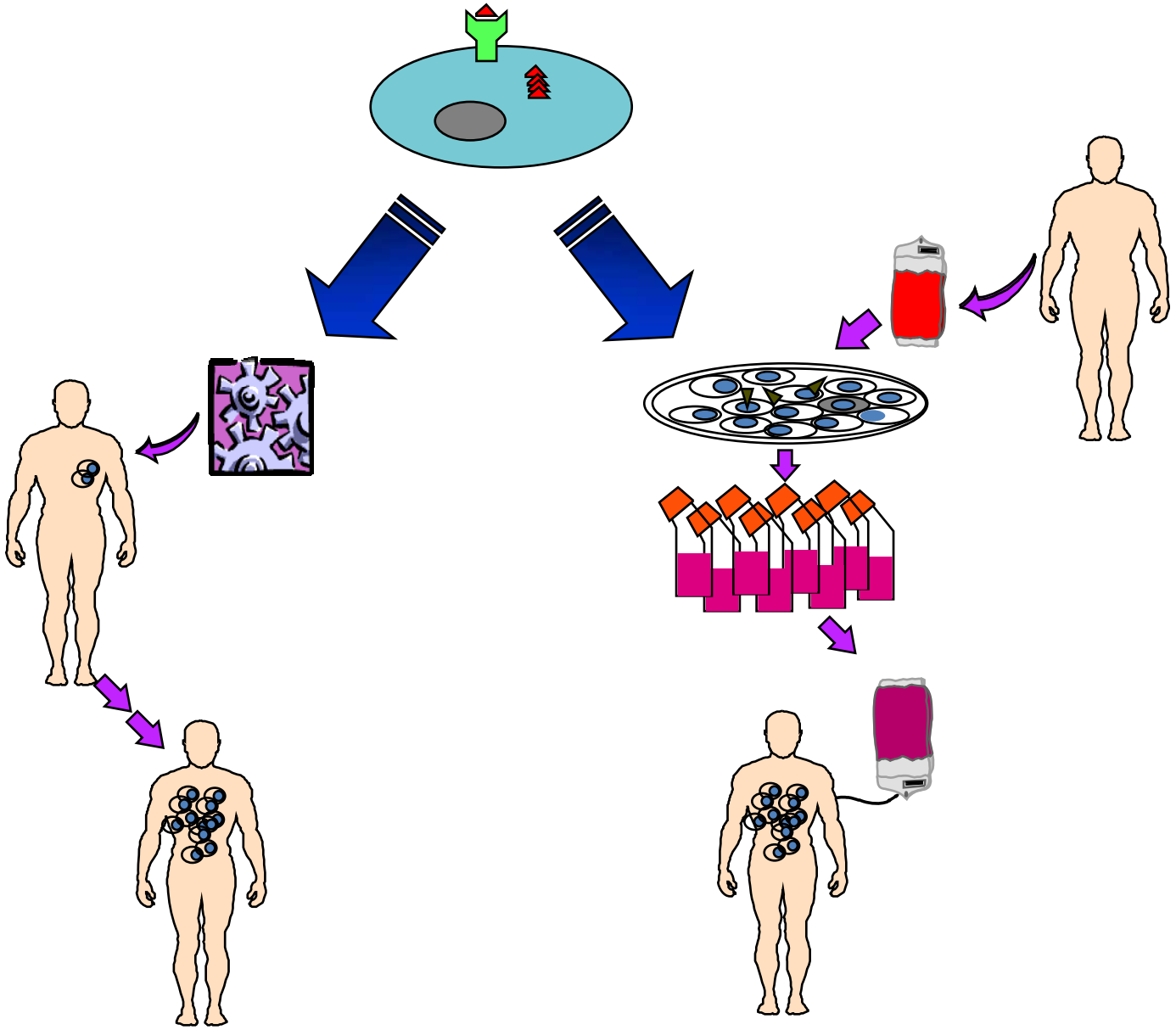
Carl June is Richard W. Vague Professor in Immunotherapy, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania.

In previous studies with Nan-ping Weng and Richard Hodes [at the US National Institutes of Health], we found that the replicative capacity of memory and naive T cells decreases with age. Thus, it is possible that T cells from aged patients may be less potent than those from younger patients.

Beyond lymphomas and melanomas, are there certain cancers that would be particularly challenging targets for T-cell therapy?

SAR: This whole area of genetically engineering of lymphocytes to express either conventional αβ T-cell receptors or CARs [chimeric antigen receptors] is a way to expand the range of immunotherapy to other cancer types. That was first shown in our papers in *Blood* [**116**: 4099–4102, 2010] and the *Journal of Clinical Oncology* paper [**29**: 917–924, 2011]. You can transduce chimeric receptors encoding CD19 and successfully treat patients with B-cell lymphomas or traditional α-β T cell receptors and treat patients with synovial cell sarcomas.

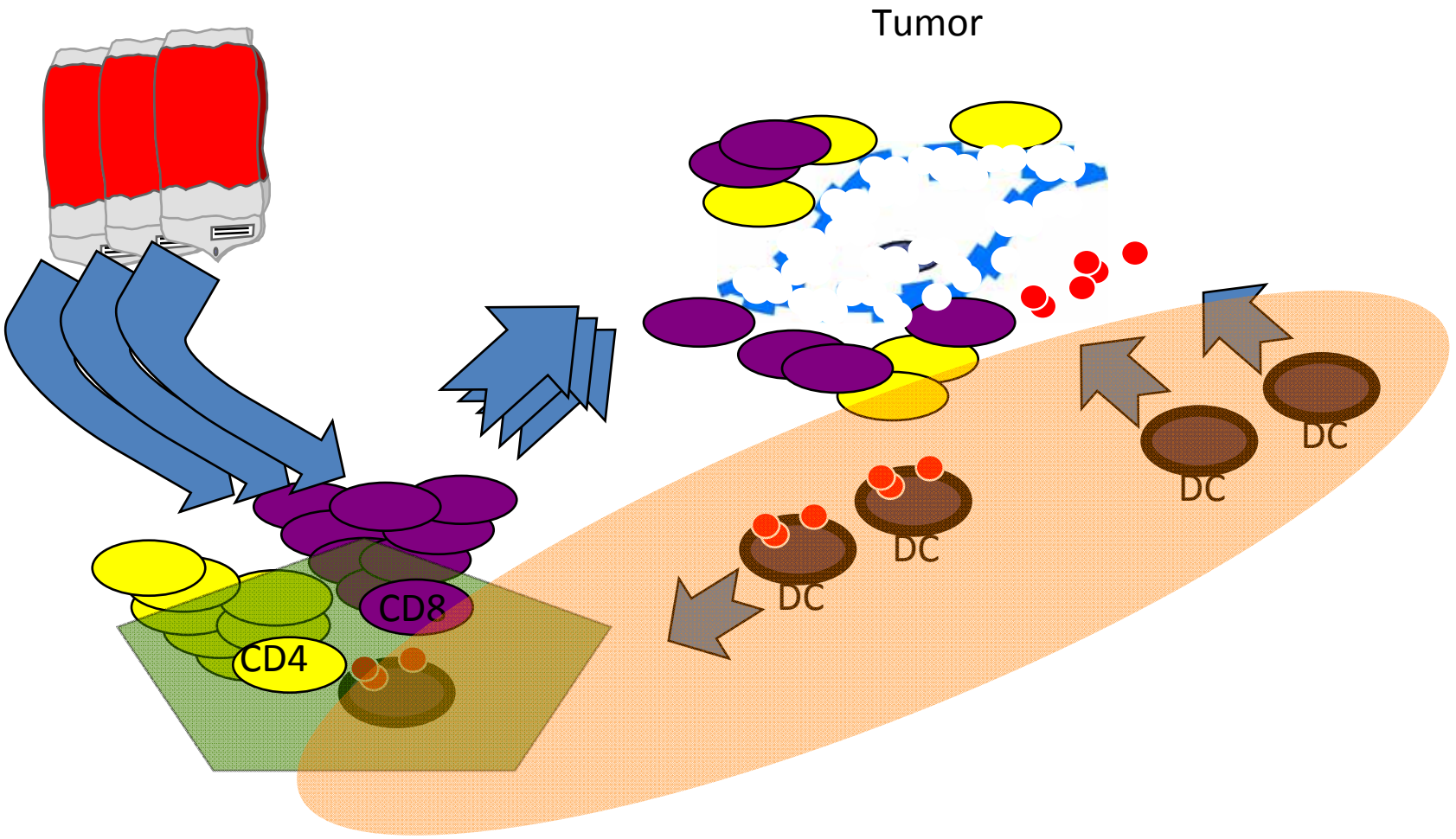
MS: There are still very few known common, tumor-specific antigens. The cancer/testes antigens are attractive, but they are inconsistently expressed in all cases of the tumor types where they tend to appear or in all cells of positive tumors. CD19 is a great target for CAR therapy, but few other cell-surface molecules possess such a favorable profile—high expression on most tumor cells and expression in normal cells restricted to a dispensable cell type. Target identification remains a major research goal.



Vaccine Therapy

Adoptive Therapy

Adoptive T Cell Therapy



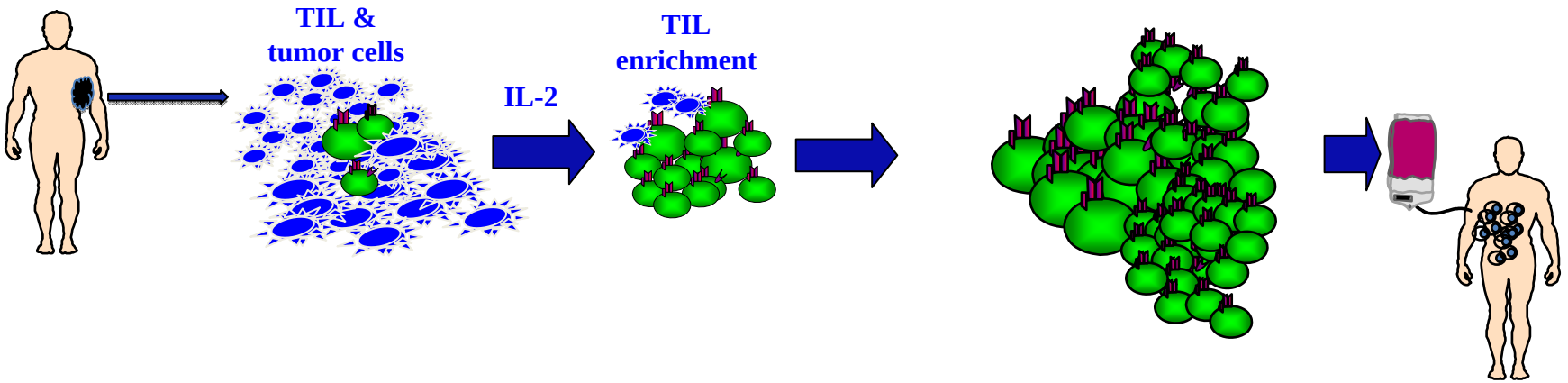
Choice of Effectors

TIL	Transferred Receptors CAR/TCR	Endogenous Receptor

Choice of Effectors

TIL	Transferred Receptors CAR/TCR	Endogenous Receptor

Tumor Infiltrating Lymphocytes (TILs)



Melanoma
RCC

Ovarian
Breast
Colorectal

Tumor Infiltrating Lymphocyte

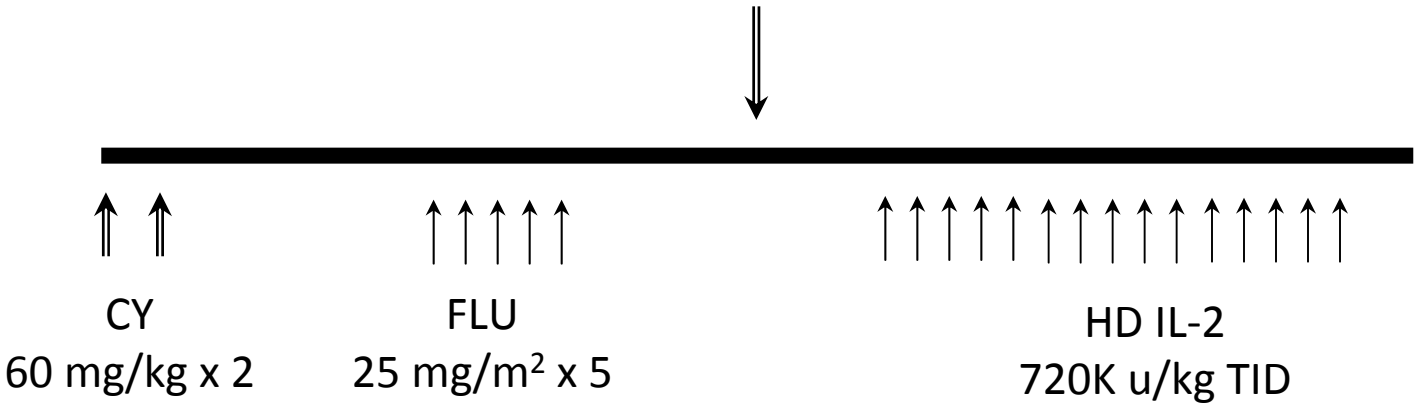
TIL	Transferred Receptors CAR/TCR	Endogenous Receptor
Requires tumor **HD IL-2 dependence**		
Least labor intensive		

Tumor Infiltrating Lymphocyte

Adoptive Therapy following
Non-myeloablative Lymphodepletion

Study Design

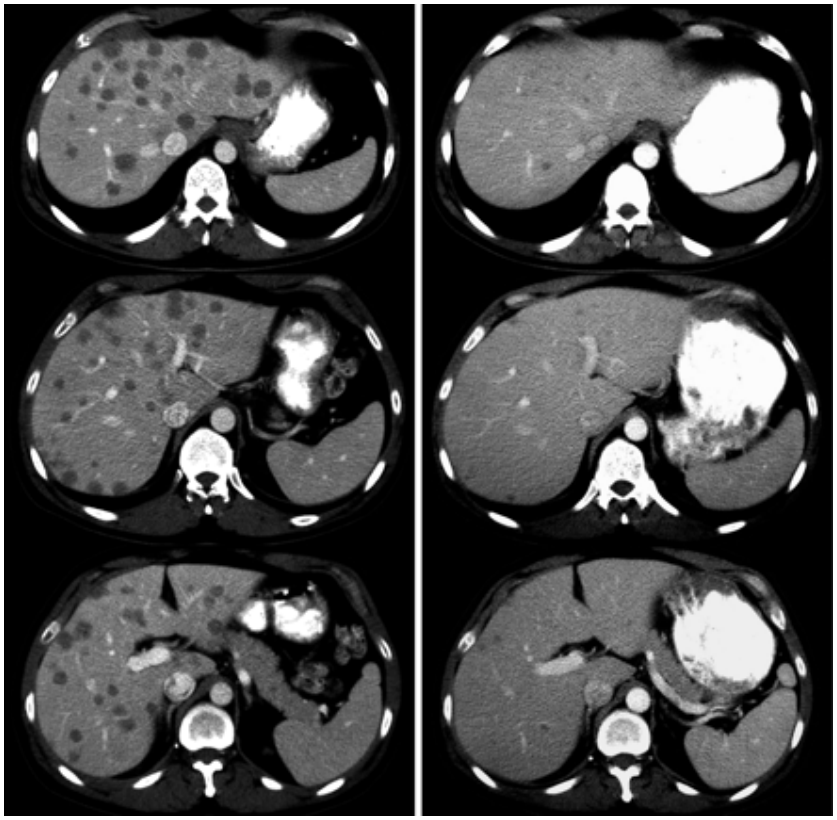
- Patients with metastatic melanoma
- Treated at time of progression, refractory disease
- TIL expanded in vitro to > 10^{10} cells



Dudley et al, Science 2002

Tumor Infiltrating Lymphocyte

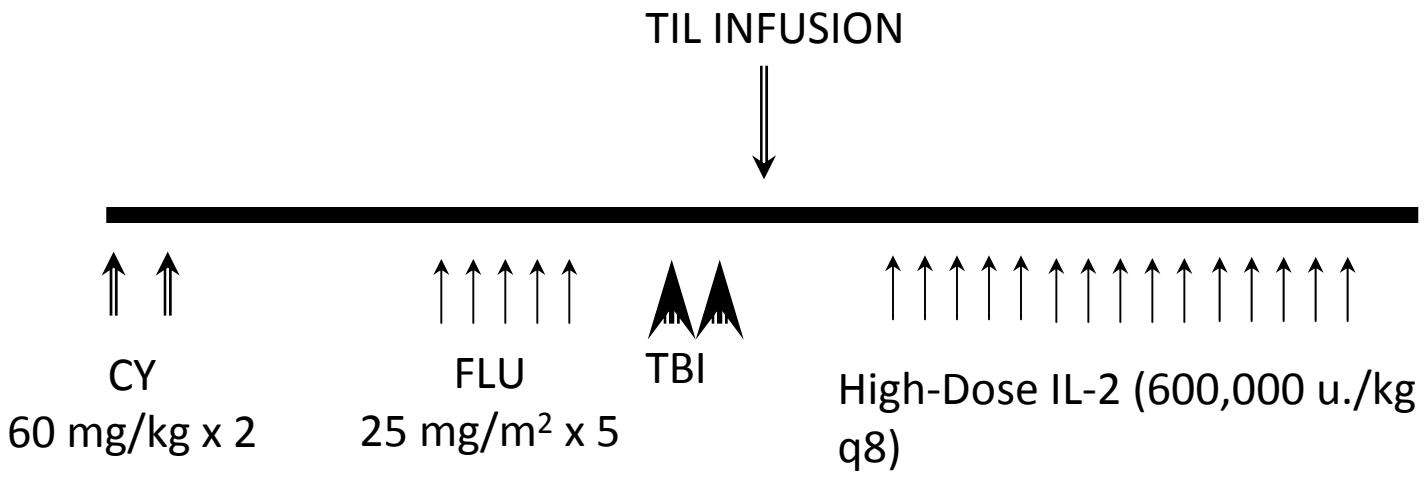
Pre- Post-



Tumor Infiltrating Lymphocyte

- 18 / 35 responders (3 CR, 15 PR)
- Serious adverse events (≥Grade 4)
  - Uveitis
  - PCP
  - EBV-LPD
  - Intubation
- Clonal response at tumor site

Tumor Infiltrating Lymphocyte

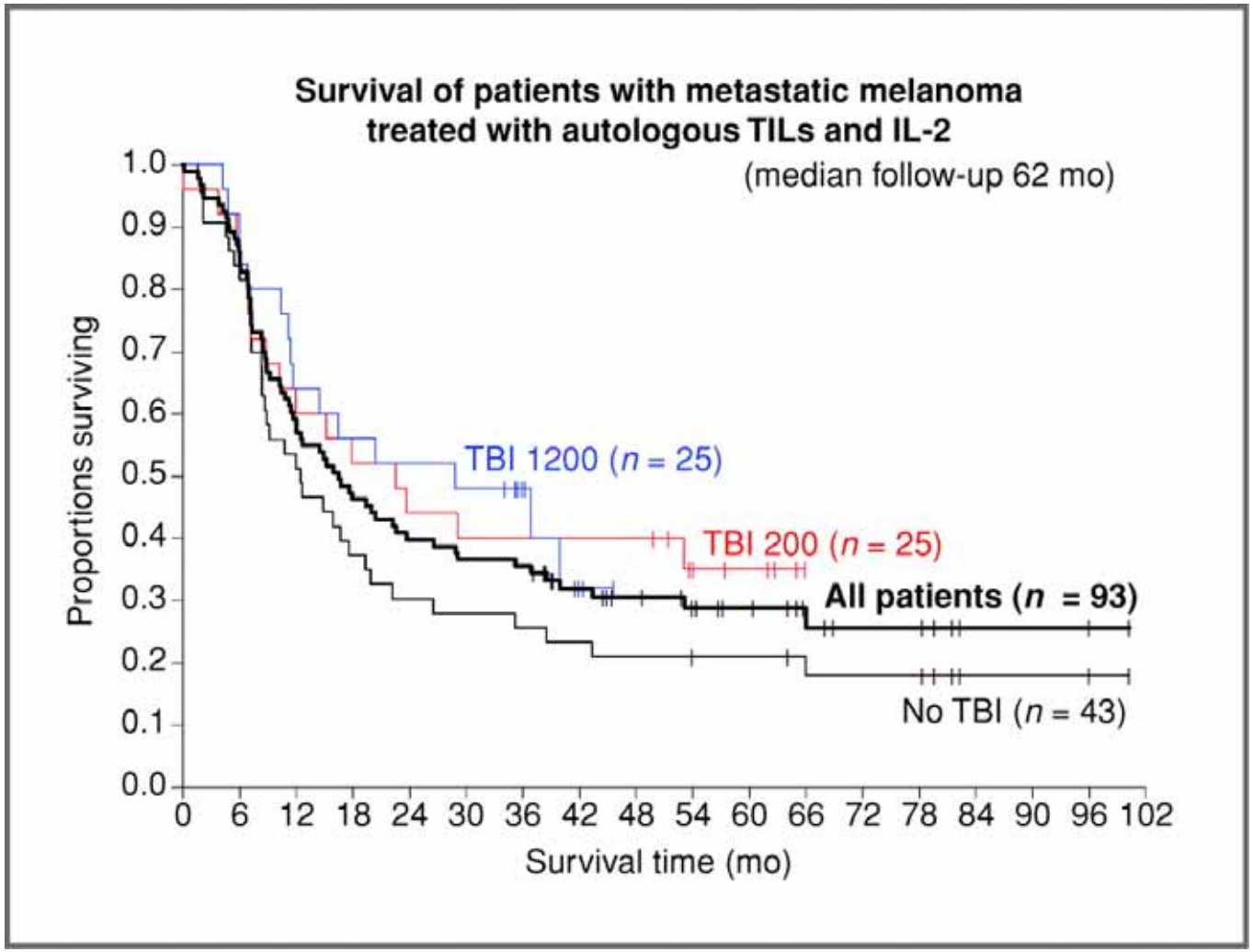


Tumor Infiltrating Lymphocyte

Treatment	*n* (%) of patients (duration in mo)			OR (%)
	Total	PR	CR	
No TBI	43	16 (37)	5 (12)	21 (49)
		84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 7, 4, 4, 2, 2, 2	82+, 81+, 79+, 78+, 64+	
200 TBI	25	8 (32)	5 (20)	13 (52)
		14, 9, 6, 6, 5, 4, 3, 3	68+, 64+, 60+, 57+, 54+	
1,200 TBI	25	8 (32)	10 (40)	18 (72)
		21, 13, 7, 6, 6, 5, 3, 2	48+, 45+, 44+, 44+, 39+, 38+, 38+, 38+, 37+, 19	
Total	93	32 (34)	20 (22)	52 (56)

Tumor Infiltrating Lymphocyte

Overall survival of patients receiving TILs with the chemotherapy preparative regimen alone (no TBI) or plus 2 or 12 Gy TBI.



Rosenberg S A et al. Clin Cancer Res 2011;17:4550-4557

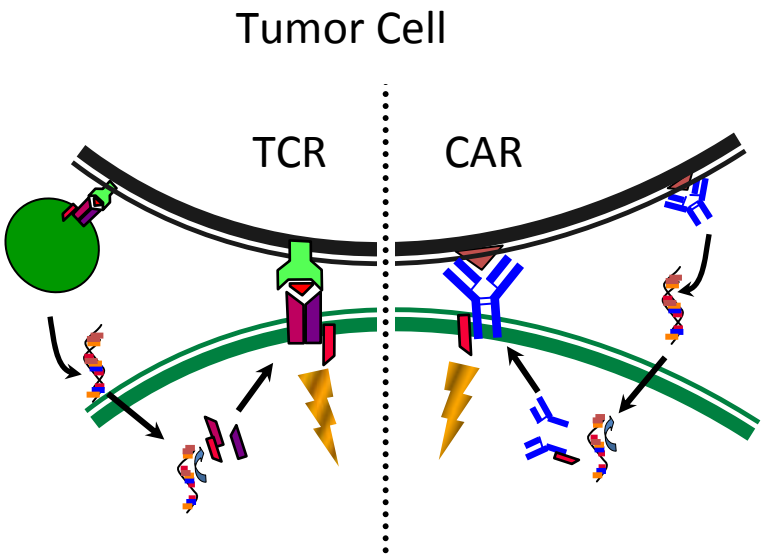
Tumor Infiltrating Lymphocyte

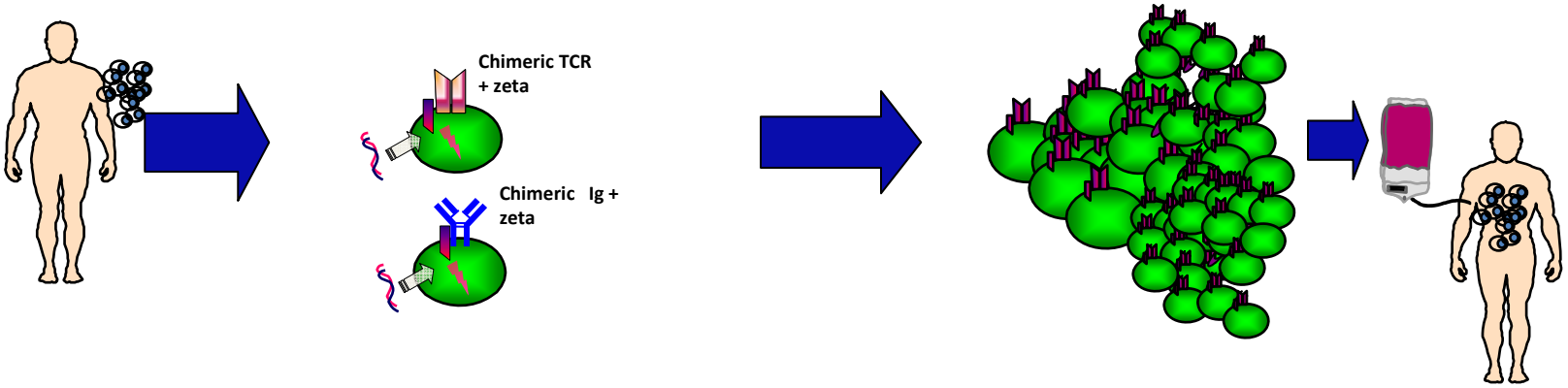
- Significant responses
- Durability?
- Patient eligibility
- Facilities available
- 2nd and 3rd generation TIL
  - Gene-modification
  - Selection

Choice of Effectors

TIL	Transferred Receptors CAR/TCR	Endogenous Receptor
Requires tumor **HD IL-2 dependence**	**Transduction efficiency** **Regulatory approval**	
Least labor intensive	**Uniform specificity** **Most efficient**	

Transferred Receptor: TCR / CAR



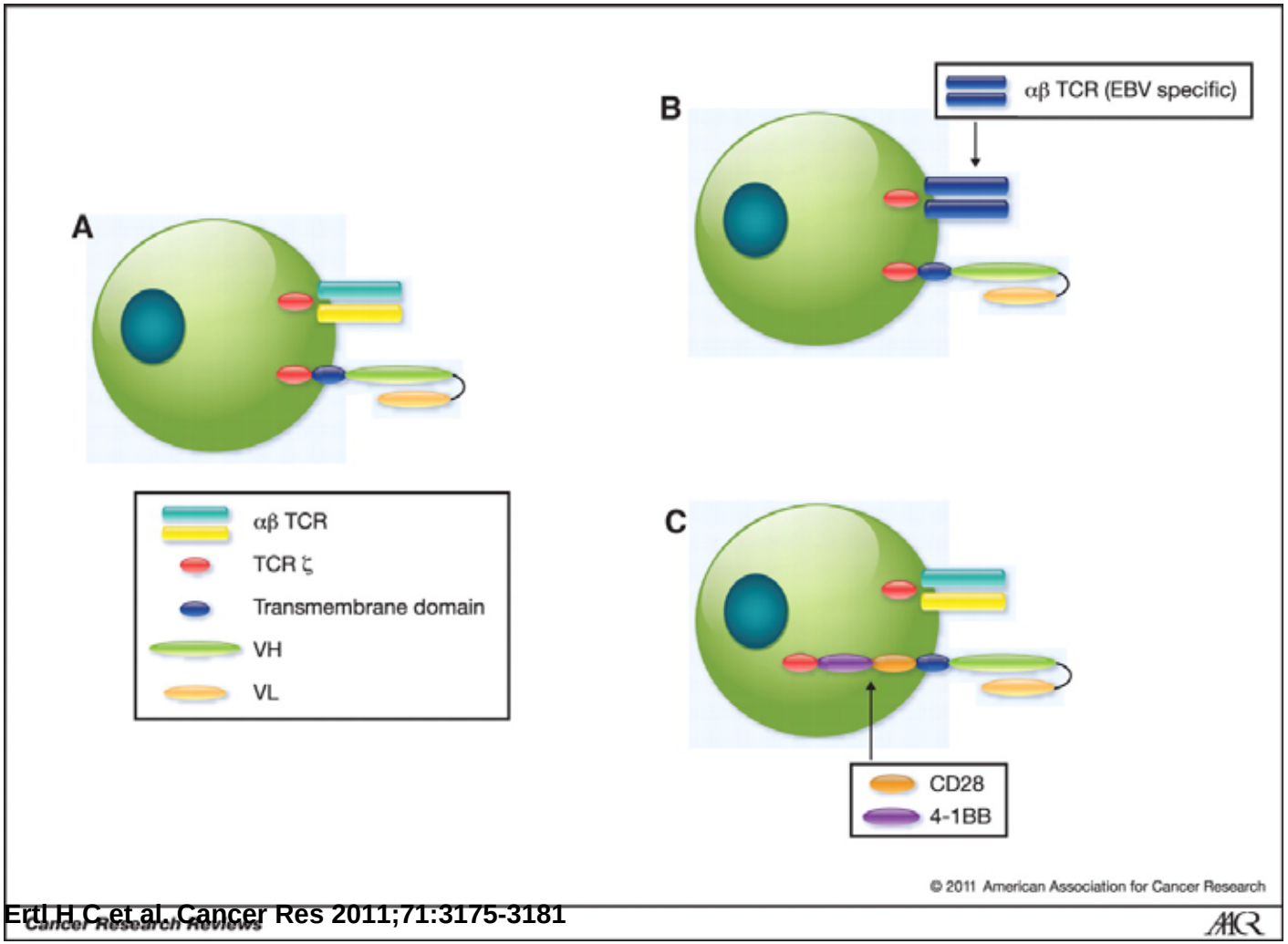


Receptor Transfer

T Cell Expansion & Infusion

Transferred Receptor: TCR / CAR

Requirement for a costimulatory signal



Ertl H C et al. Cancer Res 2011;71:3175-3181

Transferred Receptor: TCR / CAR

Anti-CD19-4-1BBz

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia
David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.
N. Engl J Med 2011; 365:725-733

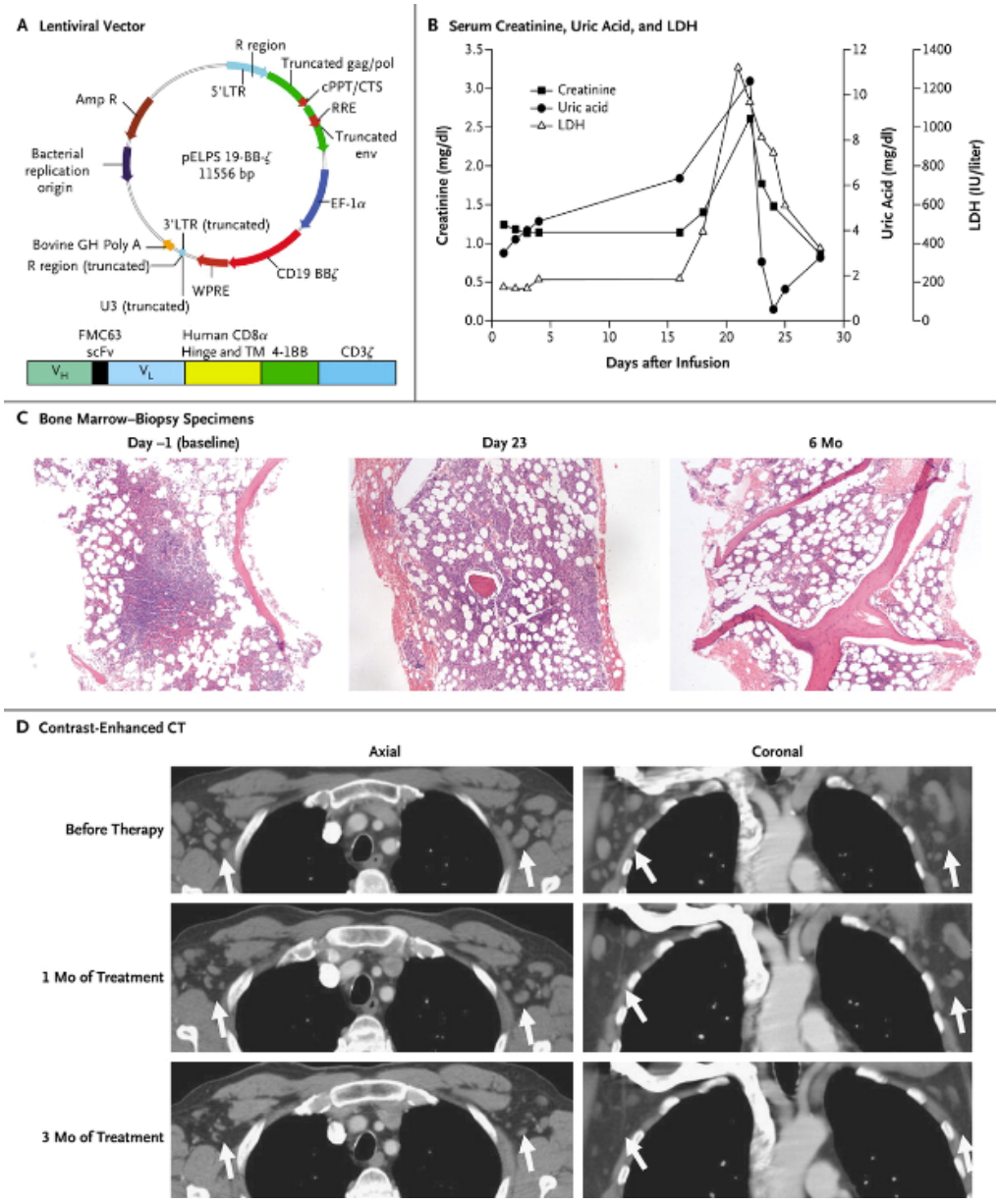
T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia
Michael Kalos, Bruce Levine, David Porter, Sharyn Katz, Stephan Grupp, Adam Bagg, Carl H. June
Sci Transl Med 10 August 2011: Vol. 3, Issue 95, p. 95ra73

3 Patients with advanced CLL. Lymphodepltion but no IL-2 post-infusion
CAR: anti-CD19 + CD137/CD3-zeta

BM 70% CLL	Bendamustine	1.6 x 10^7	CR
BM 95% CLL	Bendamustine /Rituximab	1.0 x 10^6	PR
BM 40% CLL	Pentostatin/CTX	1.5 x 10^5	CR (Tumor lysis)

Persist > 6 months, > 1000-fold expansion, >1000:1 killing, > 1 kg tumor
No immunogenicity to vector

Transferred Receptor: TCR / CAR



Transferred Receptor: TCR / CAR

Anti-CD19-CD28z

Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias.
Blood. 2011 Nov 3;118(18):4817-28. Brentjens RJ…Sadelain M

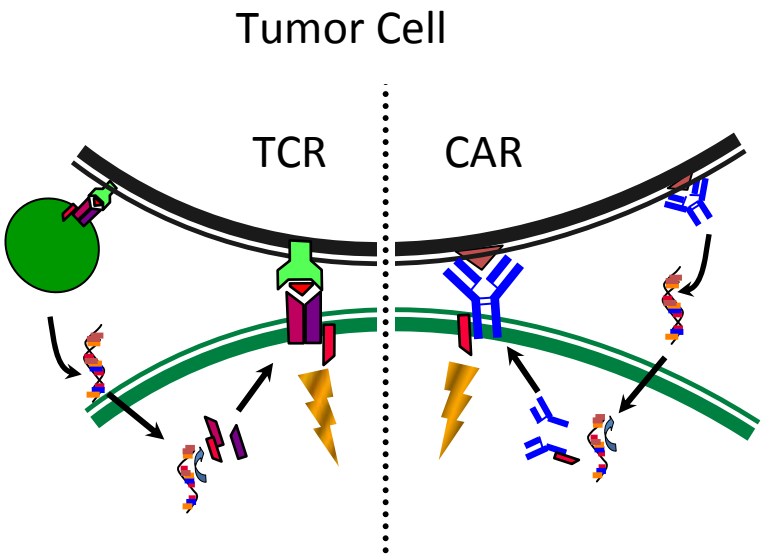
Anti-CD19-CD28/zeta

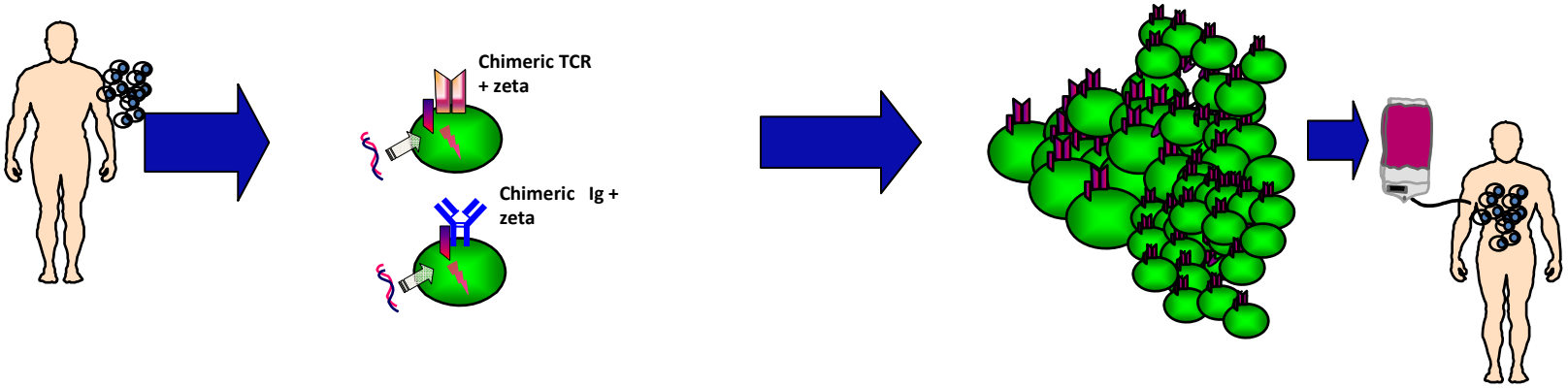
10 patients

Up to 3 x 10^7/kg +/- cyclophosphamide conditioning
no post-infusion IL-2

8/9 well toelrated
3 of 3 with bulky CLL + CY conditioning -> (1 PR, 2 SD)
Persistence 4-6 weeks in 2/7 by BM
Persistence copy number .01 – 1.0/ 100 cells 30 days+

Transferred Receptor: TCR / CAR





Receptor Transfer

T Cell Expansion & Infusion

Transferred Receptor: TCR / CAR

Target Antigen/ Cancer

Antigen	CAR or TCR	Cancer
MART-1, gp100	TCR	Melanoma
NY-ESO-1	TCR	Sarcoma, Myeloma, (Breast, Lung)
MAGE-A3	TCR	Any cancer MAGE-A3+
P53	TCR	Any cancer overexpress p53
CD19	CAR	Lymphoma
EGFRvIII	CAR	Glioblastoma, Breast, Lung
Kappa Light Chain	CAR	CLL, B cell NHL
Her2Neu	CAR	Osteosarcoma, Breast
CD30	CAR	Lymphoma (NHL and HD)
GD2	CAR	EBV-specific CTL targeting GBM

Transferred Receptor: TCR / CAR

Completed Clinical Studies

Science
AAAS

Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes
Richard A. Morgan *et al.*
Science **314**, 126 (2006);
DOI: 10.1126/science.1129003

Review

Trends in Biotechnology November 2011, Vol. 29, No. 11

Table 1. Recent Clinical Success using Gene Modified T Cells

Cancer	Target Antigen	Gene-Vector	Comments	Reference
Neuroblastoma	GD2	CAR-RTV	Cell persistence better in viral-specific CTL	Pule et al., 2008
Indolent B-NHL and mantle cell lymphoma	CD20	CAR-EP	Successful demonstration of non-viral gene transfer	Till et al., 2008
Melanoma	MART-1	TCR-RTV	30% response rate with on-target/off-tumor toxicity	Johnson et al., 2009
Melanoma	gp100	TCR-RTV	19% response rate with on-target/off-tumor toxicity	Johnson et al., 2009
Lymphoma	CD19	CAR-RTV	Near complete response with concomitant elimination of B cells.	Kochenderfer et al., 2010
Colorectal cancer	CEA	TCR-RTV	Responses associated with on-target/off-tumor toxicity	Parkhurst et al., 2010
Synovial sarcoma and melanoma	NY-ESO-1	TCR-RTV	50% response rate with no toxicity.	Robbins et al., 2011

Abbreviations; CAR, Chimeric Antigen Receptor; TCR, T Cell Receptor; RTV, gamma-retroviral vector; EP, electroporation.

Transferred Receptor: TCR / CAR

Molecular Construct Issues

- CAR/TCR: affinity
  - Phage display, mutations
  - HSC, iPS + Notch ligand
- TCR: pairing
  - Disulfide, murine, zipper
- Transfection efficiency
  - Lentiviral, SB transposon
- Cell type
  - ?
- Immunogenicity

Transferred Receptor: TCR / CAR

Clinical Issues

- Cytokine release syndrome toxicity
- On-target Toxicities

- Minimize/escalate conditioning
- Dose escalation
- Split infusion dosage

Choice of Effectors

TIL	Transferred Receptors CAR/TCR	Endogenous Receptor

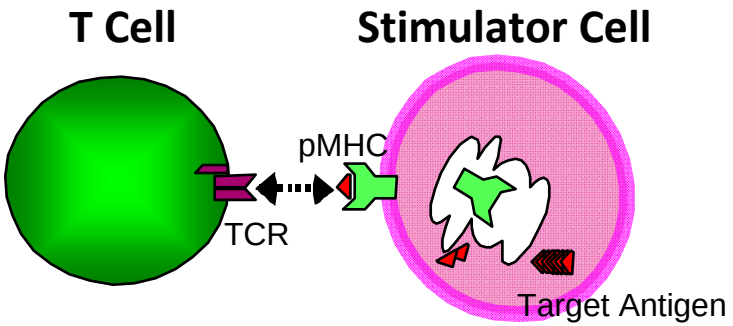
Choice of Effectors

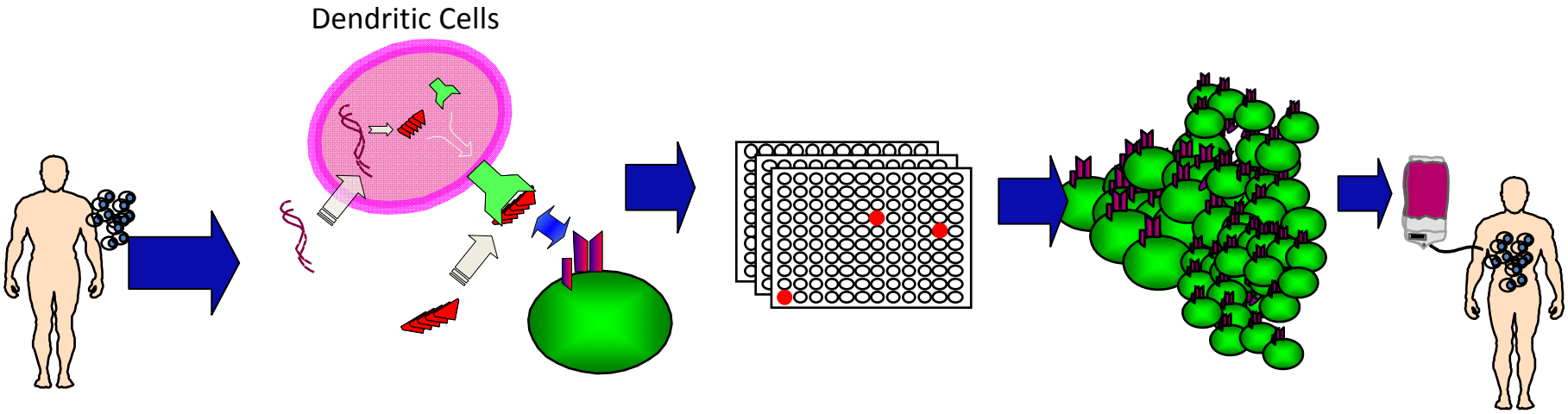
TIL	Transferred Receptors CAR/TCR	Endogenous Receptor

Choice of Effectors

TIL	Transferred Receptors CAR/TCR	Endogenous Receptor
Requires tumor **HD IL-2 dependence**	**Transduction efficiency** **Regulatory approval**	**Labor-intensive**
Least labor intensive	**Uniform specificity** **Most efficient**	**Most physiologic**

Endogenous Receptor



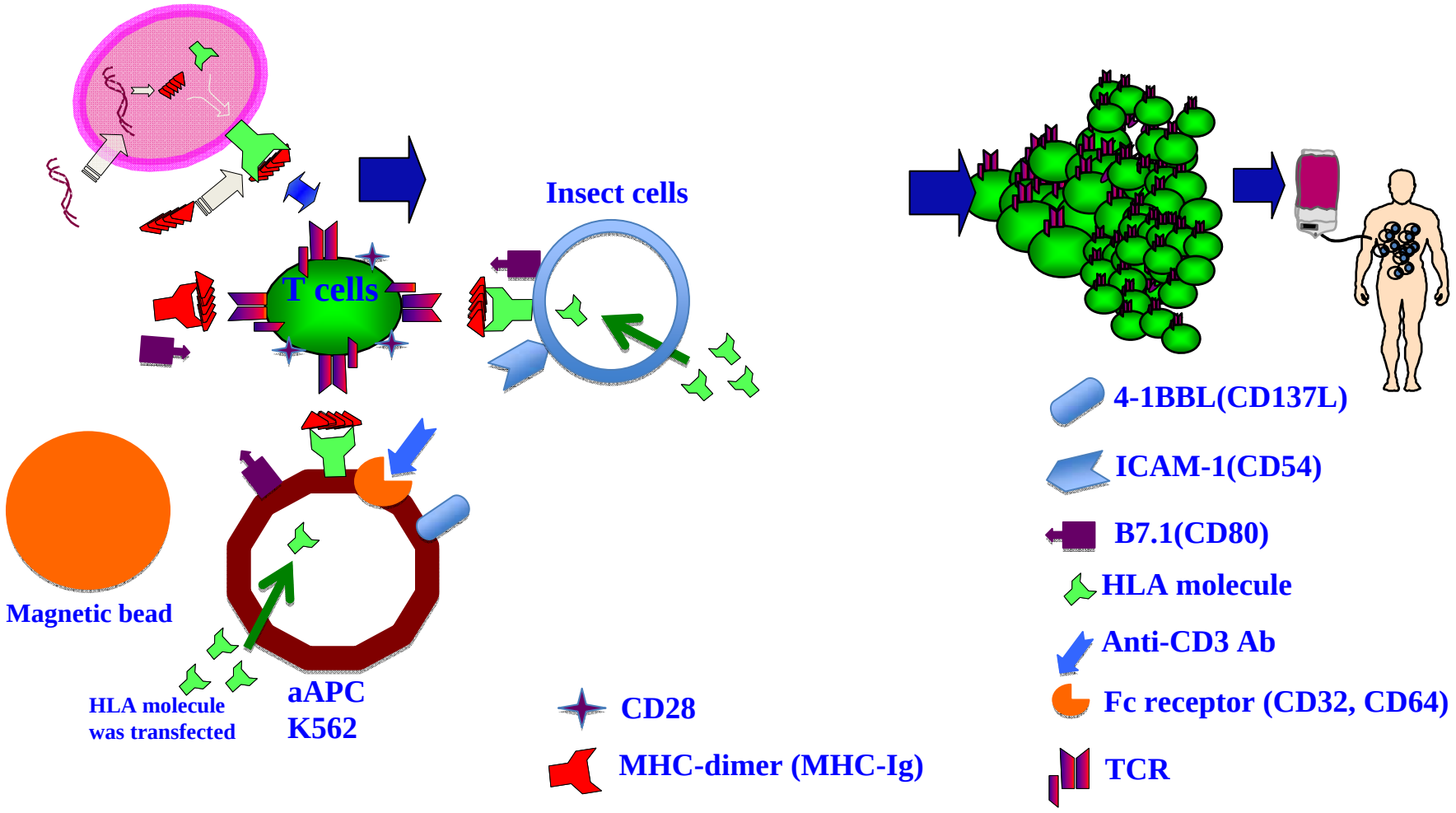


Antigen-specific
T Cell Enrichment

T Cell Expansion & Infusion

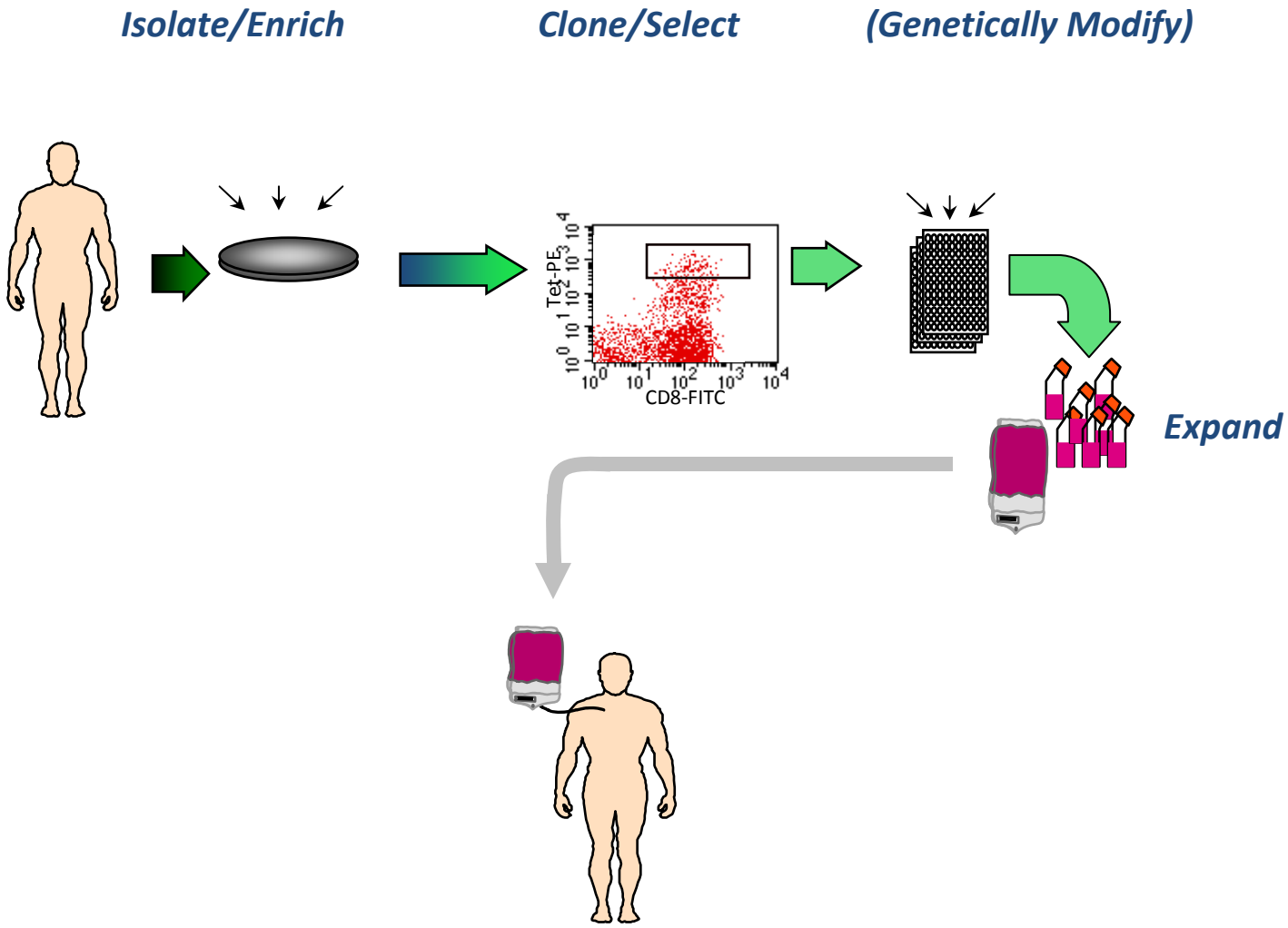
Endogenous Receptor

Artificial Antigen Presenting Cells

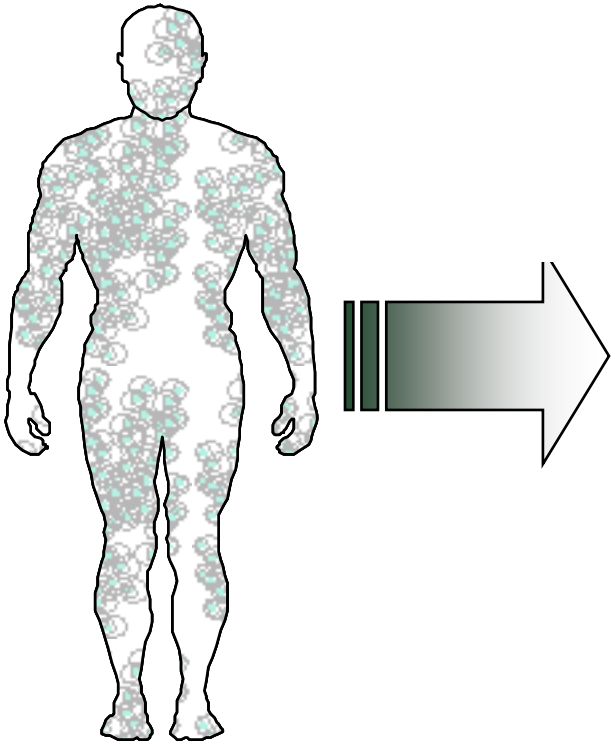


Endogenous Receptor

Adoptive T Cell Therapy: Basic Protocol



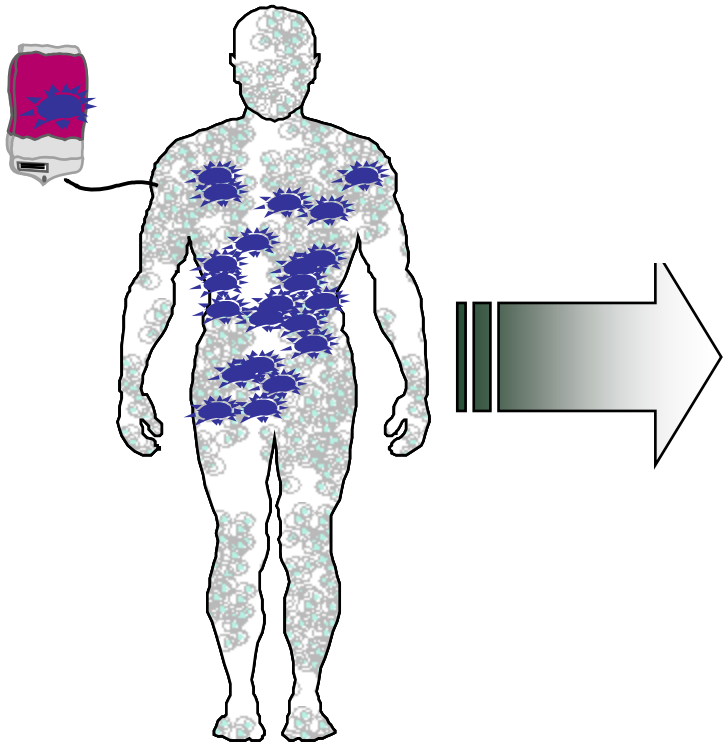
Lymphoid Homeostasis



other growth signals
other cytokines
IL-15
IL-7

Lymphodepletion

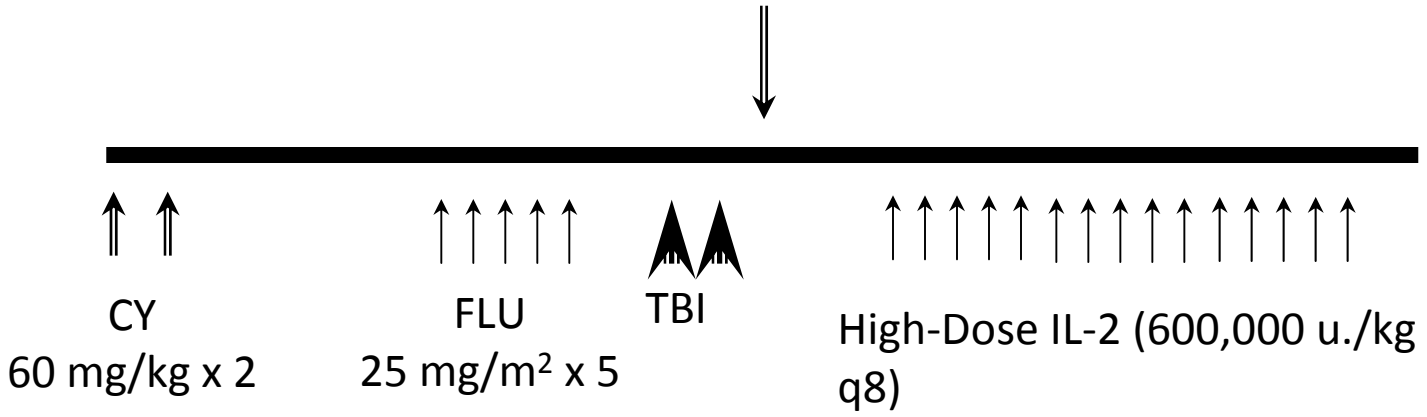
building a better environment



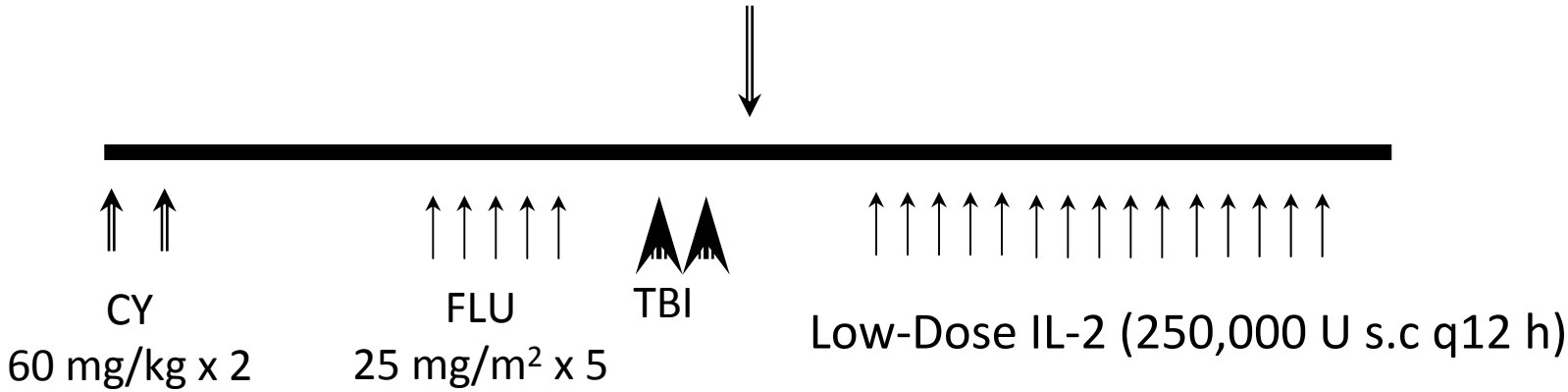
Increase 'space' for transferred T cells
Eliminate 'suppressor cells'
Supply Growth Factors

Increase 'space' for transferred T cells
Eliminate 'suppressor cells'
Supply Growth Factors

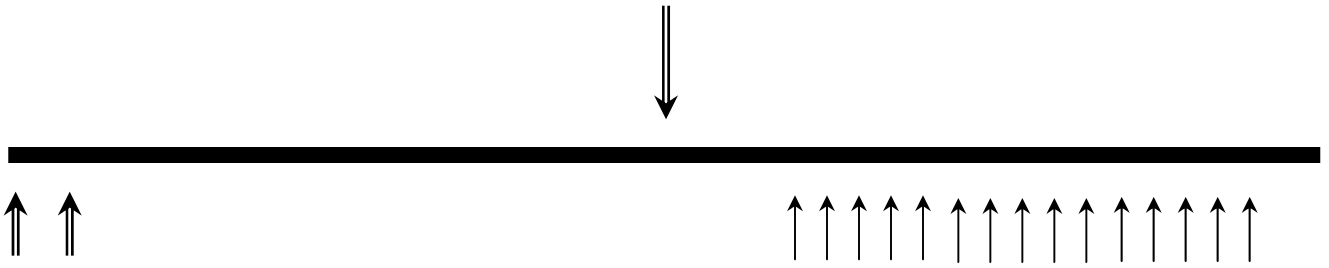
Endogenous Receptor



Endogenous Receptor



Endogenous Receptor



CY
60 mg/kg x 2

Low-Dose IL-2 (250,000 U s.c q12 h)

Objectives :
- Evaluate Safety
- Evaluate T Cell Persistence
- Evaluate anti-tumor efficacy

Eligibility Criteria :
- Stage IV (Metastatic)
- HLA-A2

T Cell Infusion:
- Antigen-specific CD8+ T cell clones
- Targeting MART-1, gp100
- Dose: 10^{10} cells / m^2

PNAS

Transferred melanoma-specific CD8$^+$ T cells persist, mediate tumor regression, and acquire central memory phenotype

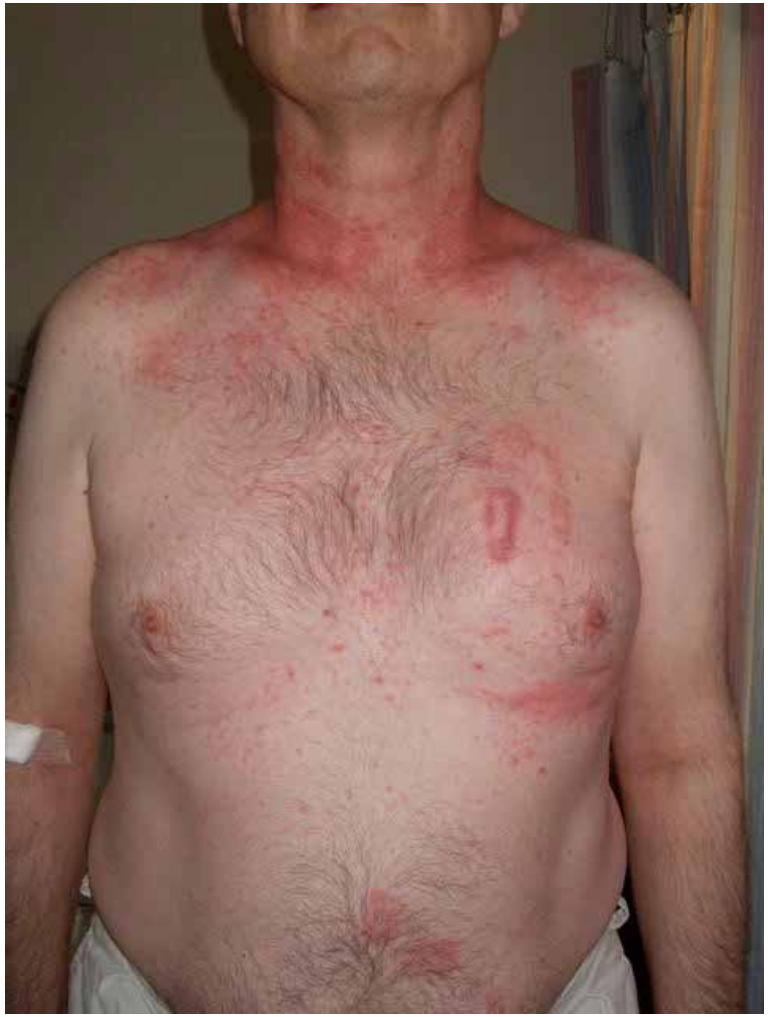
Aude G. Chapuis[a], John A. Thompson[b], Kim A. Margolin[b], Rebecca Rodmyre[a], Ivy P. Lai[a], Kaye Dowdy[a], Erik A. Farrar[a], Shailender Bhatia[b], Daniel E. Sabath[c], Jianhong Cao[a], Yongqing Li[a], and Cassian Yee[a,1]

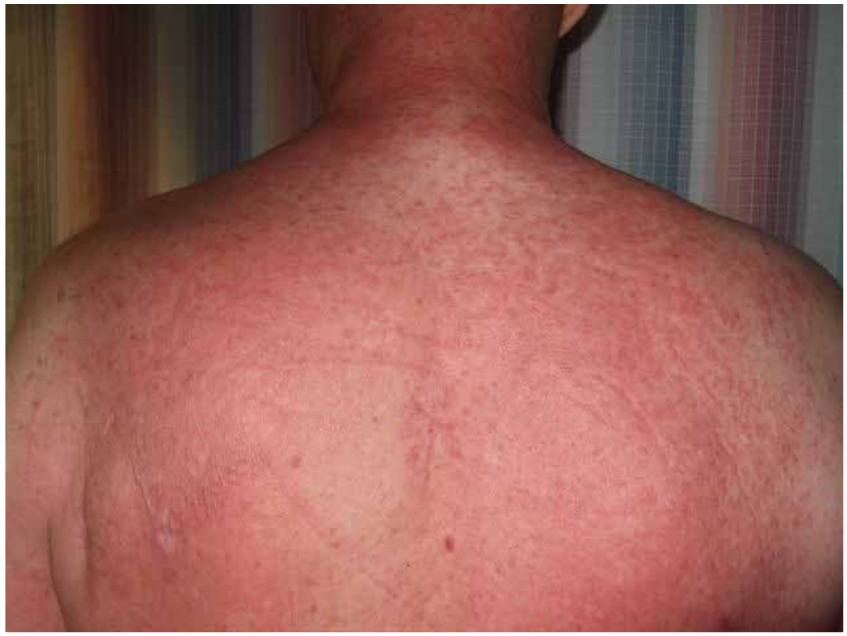
[a]Program in Immunology, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; [b]General Oncology and Hematology, Seattle Cancer Care Alliance and University of Washington, Seattle, WA 98109; and [c]Department of Laboratory Medicine, University of Washington, Seattle, WA 98195

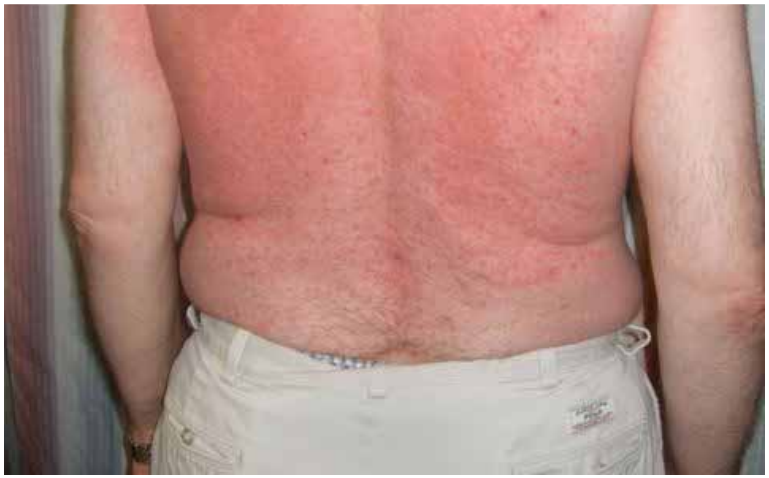
Chapuis A. et al, PNAS. March 2012

Endogenous Receptor

On-target toxicity



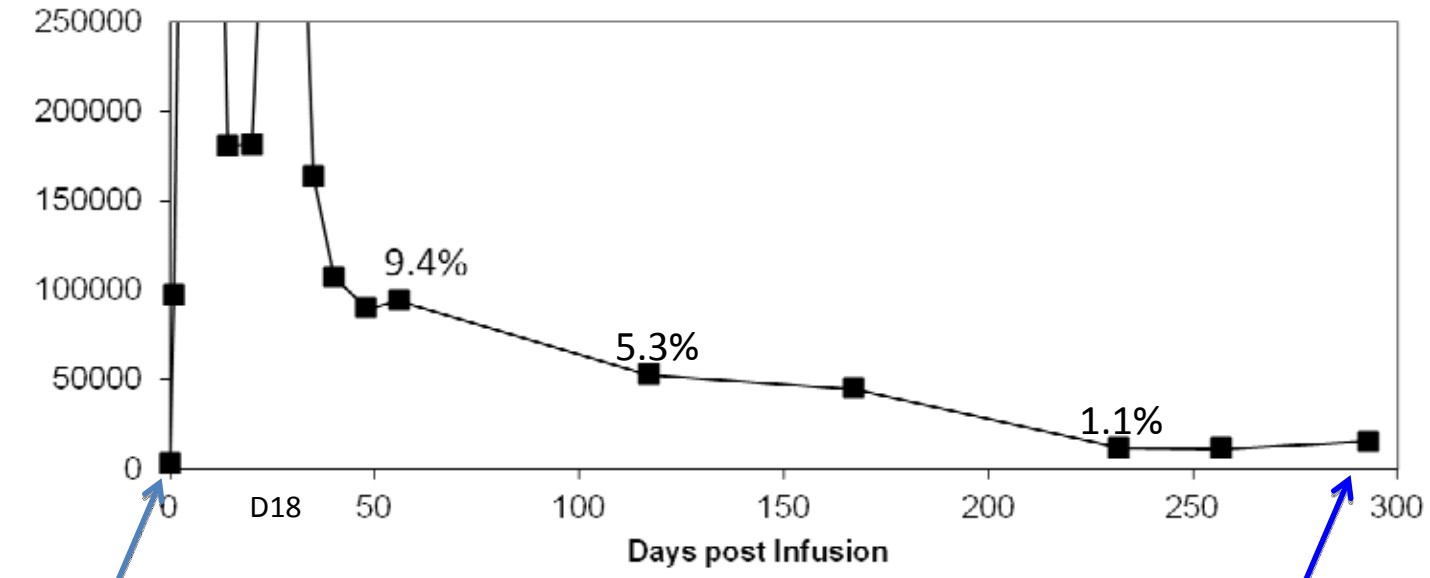




Endogenous Receptor

T cell persistence in vivo

2140-1



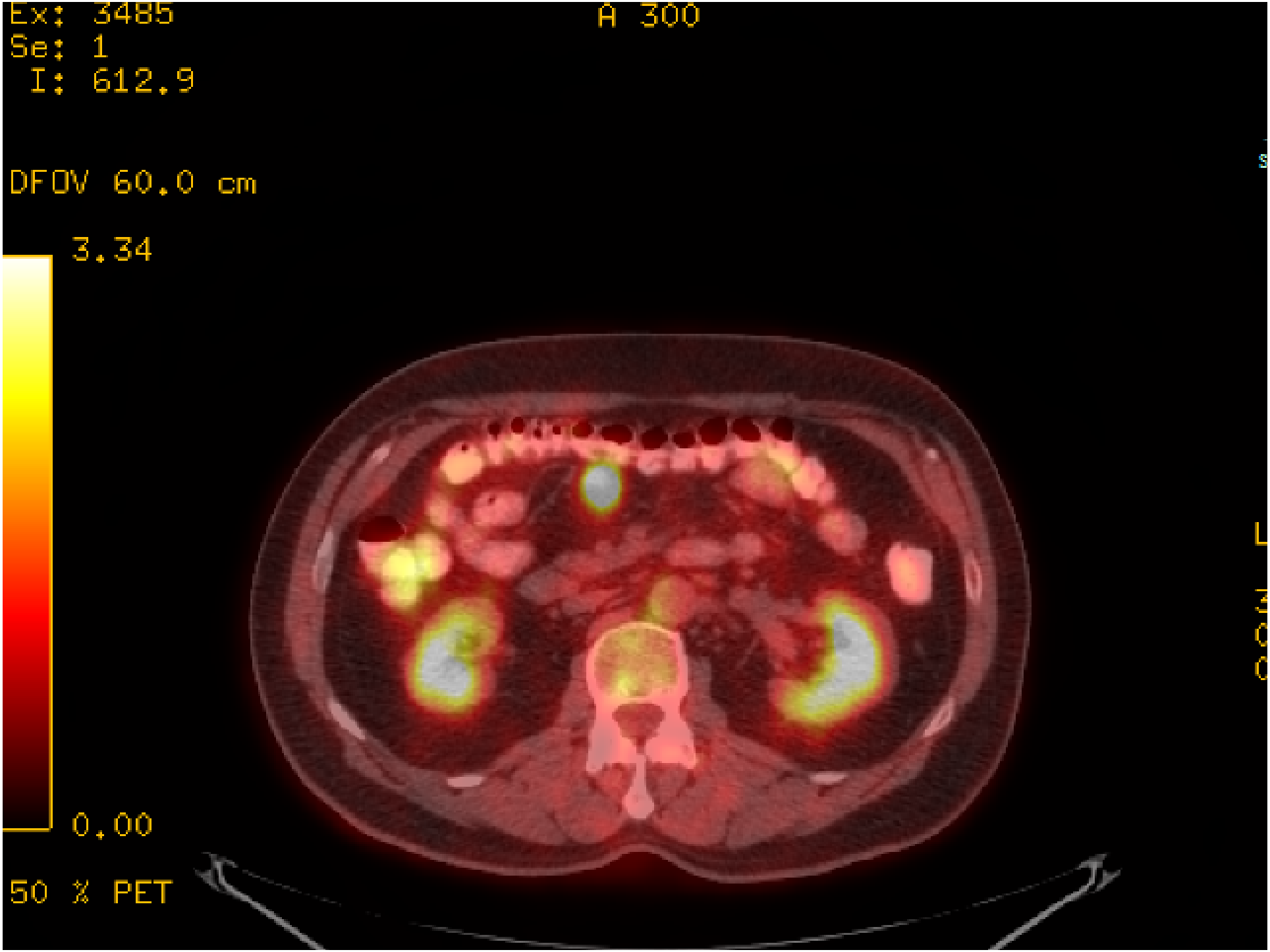
CD45 RO+
CD28-
CD127-lo

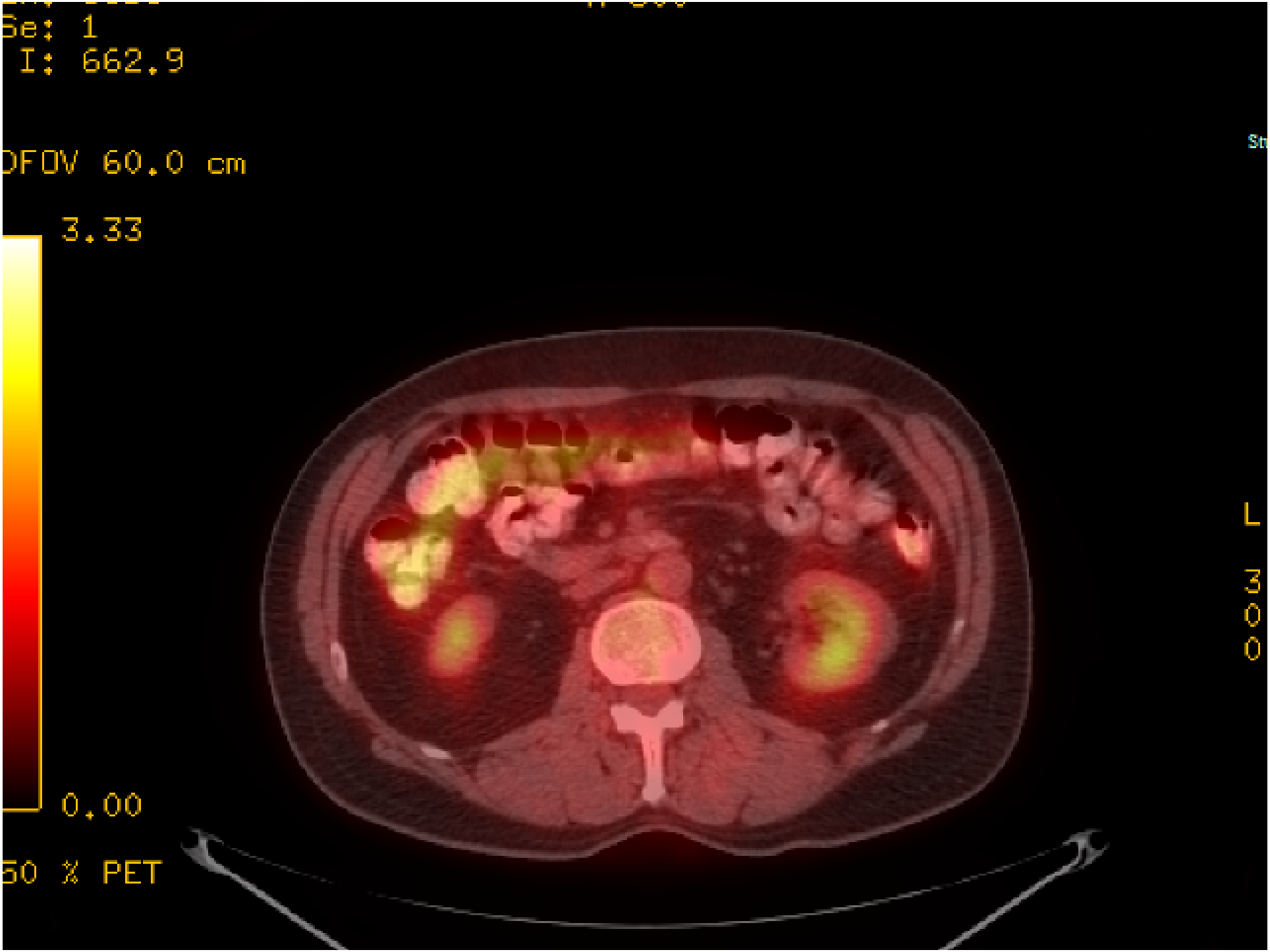
CD45 RO+
CD28++
CD127-hi

Endogenous Receptor

Clinical Response

Patient	Target	Toxicity	Persistence	Disease Sites	Response
2140-1	Tyrosinase	F,N,R	>290 days	Cervical,supraclavicular LN, Chest Wall, Breast Pulmonary nodules	MR
2140-2	Tyrosinase	F	16 days	Mediastinal, Pulmonary nodules	PD
2140-3	gp100	F,N,R	>85 days	Mesenteric LN, scapular subcutaneous dz	CR (> 12 mths)
2140-4	MART-1	F, N, R	> 30 days	Pulmonary, inguinal, subcutaneous	SD
2140-5	MART-1	F, N,R	> 30 days	Right and left kidneys, adrenal, liver	PR
2140-6	MART-1	F, N, R	> 30 days	Mediastinal, supra clavicular, mammary chain, periportal, portacaval nodes.	PR


Ex: 3485
Se: 1
I: 612.9
A 300
DFOV 60.0 cm
3.34
0.00
50 % PET


Se: 1
I: 662.9
DFOV 60.0 cm
3.33
0.00
50 % PET
L

Endogenous Receptor

Science Translational Medicine AAAS

Establishment of Antitumor Memory in Humans Using in Vitro–Educated CD8 + T Cells
Marcus O. Butler *et al.*
Sci Transl Med **3**, 80ra34 (2011);
DOI: 10.1126/scitranslmed.3002207

- aAPCs (K562, CD80, CD83, HLA-A2)
- MART-1 specific CTL + IL-2/ IL-15
- Treatment plan:
  - CTL alone (no conditioning or IL-2)

Endogenous Receptor

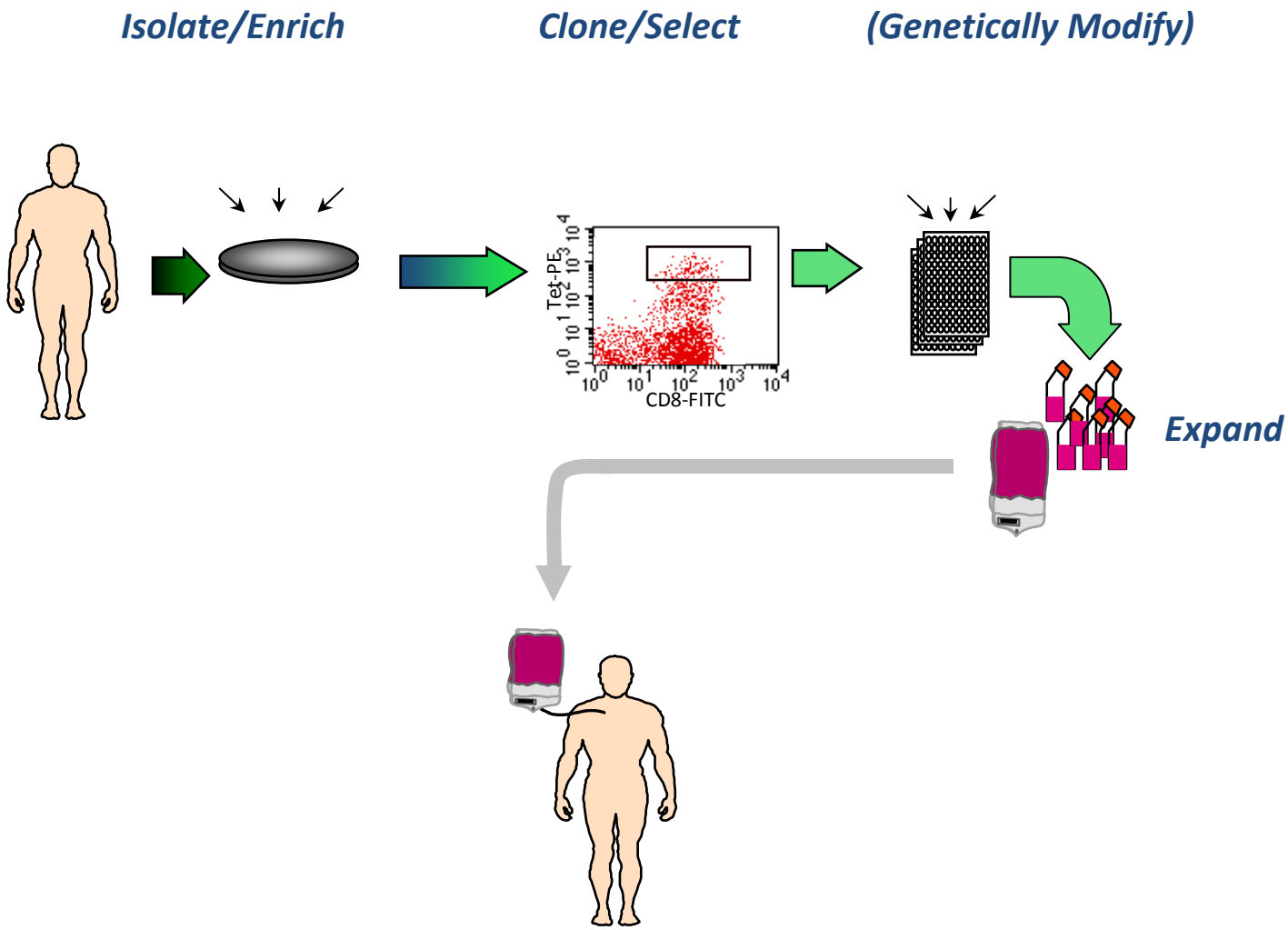
No.	Age/sex	Metastatic disease at study entry	Previous therapy	Total cells infused		Status on day 70	Time to next therapy	Outcome after CTL or next therapy	Duration of response (months)
				Graft 1	Graft 2				
1	74/M	Liver, adrenal, spleen, lung, skin	LND; carboplatin, paclitaxel, sorafenib; gp100 vaccine	4.0×10^8	None	Death on day 51	—	Died without therapy	—
2	69/M	Lung, skin	WLE; LND; temozolomide; melphalan limb perfusion	4.0×10^8	4.0×10^8	PD	Day 103 ipilimumab (10 mg/kg)	PR	16
3	49/F	Lung, adrenal	WLE; LND; RT; HD IL-2	4.3×10^8	4.3×10^8	MR	Day 146 ipilimumab (10 mg/kg)	PR	31+
4	68/M	Skeletal muscle, lung, mediastinum, cardiac	Small-bowel resection; HD IL-2; ipilimumab versus gp100 versus both	3.8×10^8	3.8×10^8	SD	Day 140 RAF265	SD	3
5	66/M	Lymph nodes	WLE; LND	4.4×10^9	2.5×10^9	PR	No other therapy	CR to CTL day 140	25+
6	55/M	Lung	WLE; LND; pulmonary nodule resection	1.8×10^9	3.4×10^9	SD	Day 287 HD IL-2	Death due to line sepsis	—
7	70/F	Lung, skin	WLE; LND; adjuvant IFN	4.0×10^9	4.0×10^9	PD	Day 335 ipilimumab (3 mg/kg)	SD	6
8	80/M	Lung, mediastinum	LND; RT; temozolomide	3.6×10^9	3.6×10^9	SD	Day 372 ipilimumab (3 mg/kg)	SD	5
9	64/M	Lung, skin	WLE; LND; adjuvant IFN	4.4×10^9	4.4×10^9	PD	Day 146 ipilimumab (10 mg/kg) +	PR	13+

Endogenous Receptor

- Effective, Relatively low toxicity
- Clinical Responses (RECIST)
- Longterm persistence
- Reversion to Memory (?)
- Effector Cell type?
- Time to generation of Effector Cells

The bigger picture…

Adoptive T Cell Therapy: Basic Protocol



PNAS Yee et al. 2002

Adoptive T Cell Therapy: Extended Protocol

Intrinsic

Isolate/Enrich

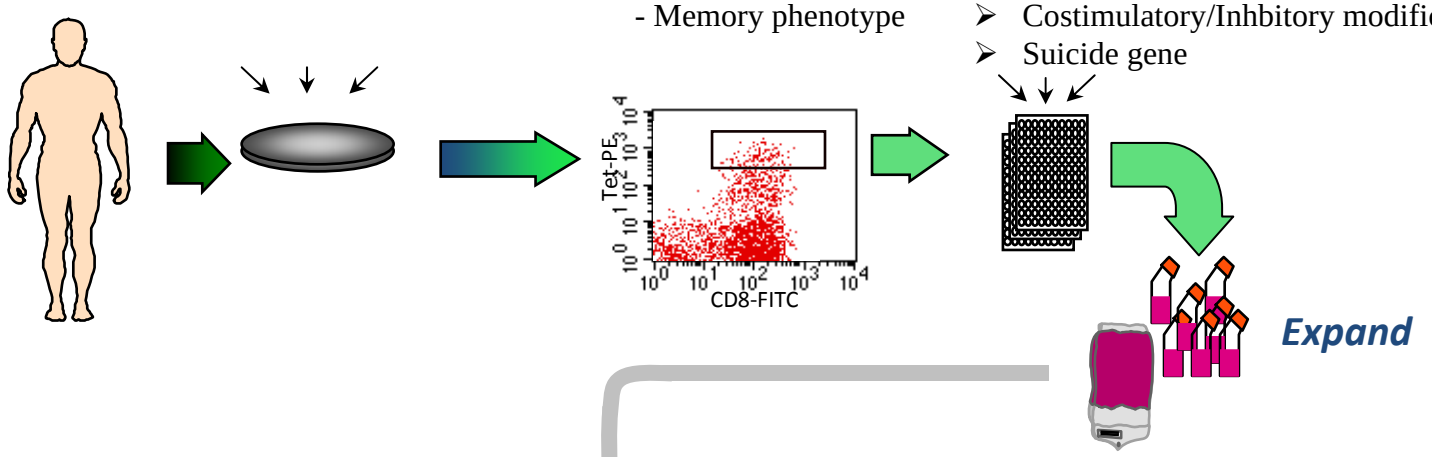
- Cytokine modulation

Clone/Select

- Phenotype
  - CD8/CD4
  - Memory phenotype

Genetically Modify

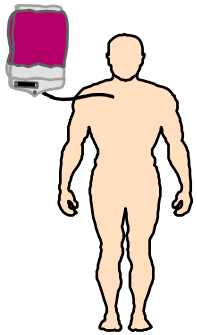
- TCR
- Chimeric receptor
- Costimulatory/Inhbitory modification
- Suicide gene



Extrinsic

Pre-infusion Immunomodulation

- Lymphodepletion
  - Chemotherapy/TBI



Post-infusion Immunomodulation

- Cytokine help
  - Low-dose IL-2
  - High-dose IL-2
  - Other γ-chain receptor cytokines
- Anti-CTLA4, Anti PD-1
- Vaccine + adoptive therapy

Hematol Oncol Clin North Am. 2006 Jun;20(3):711-3

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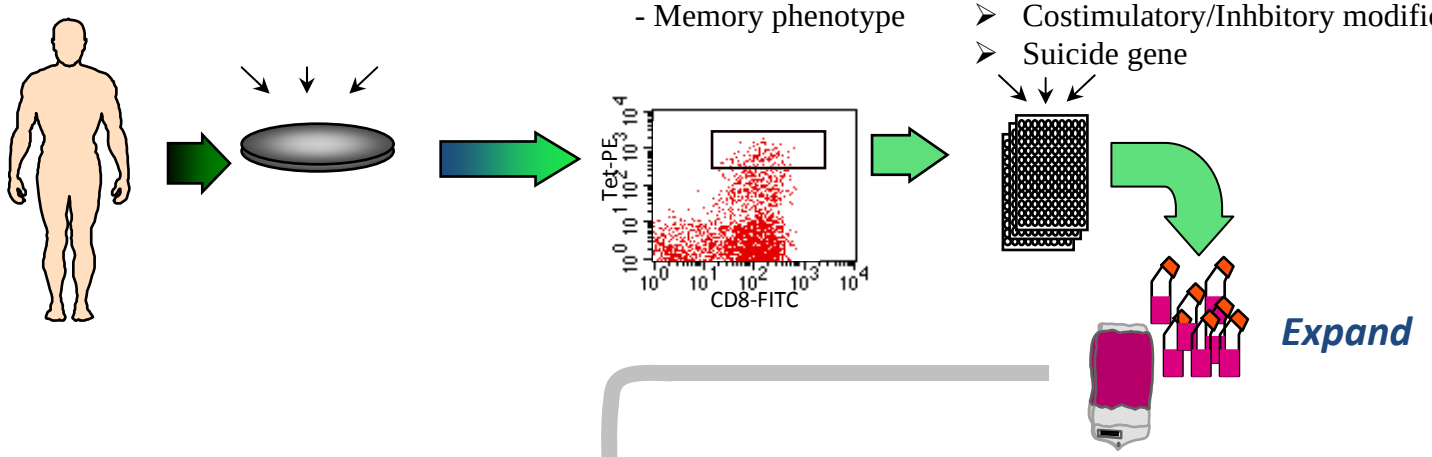

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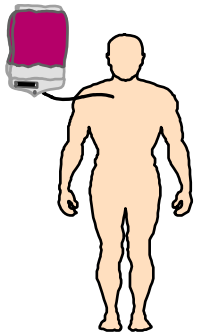

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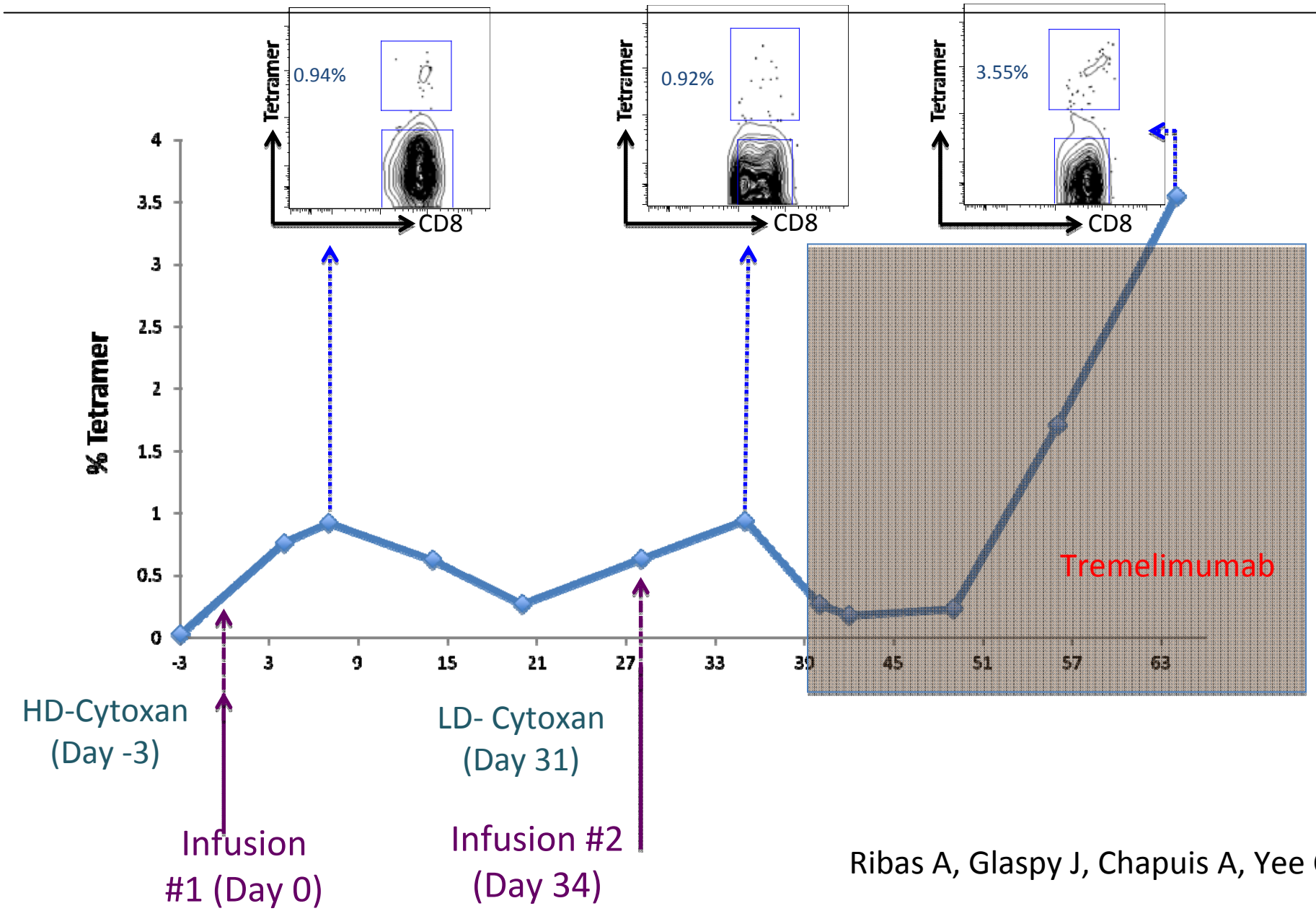
Metastatic breast cancer, NY-ESO-1+, T-cells targeting HLA A*2402/NY-ESO-1



Ribas A, Glaspy J, Chapuis A, Yee C

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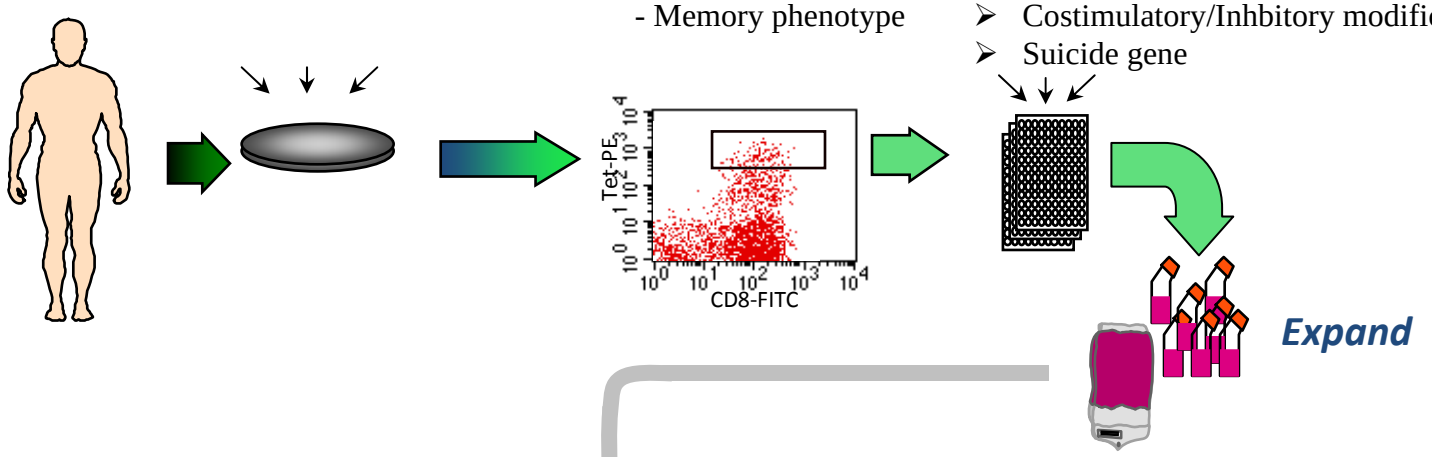

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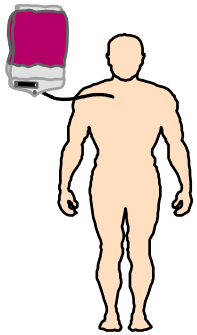

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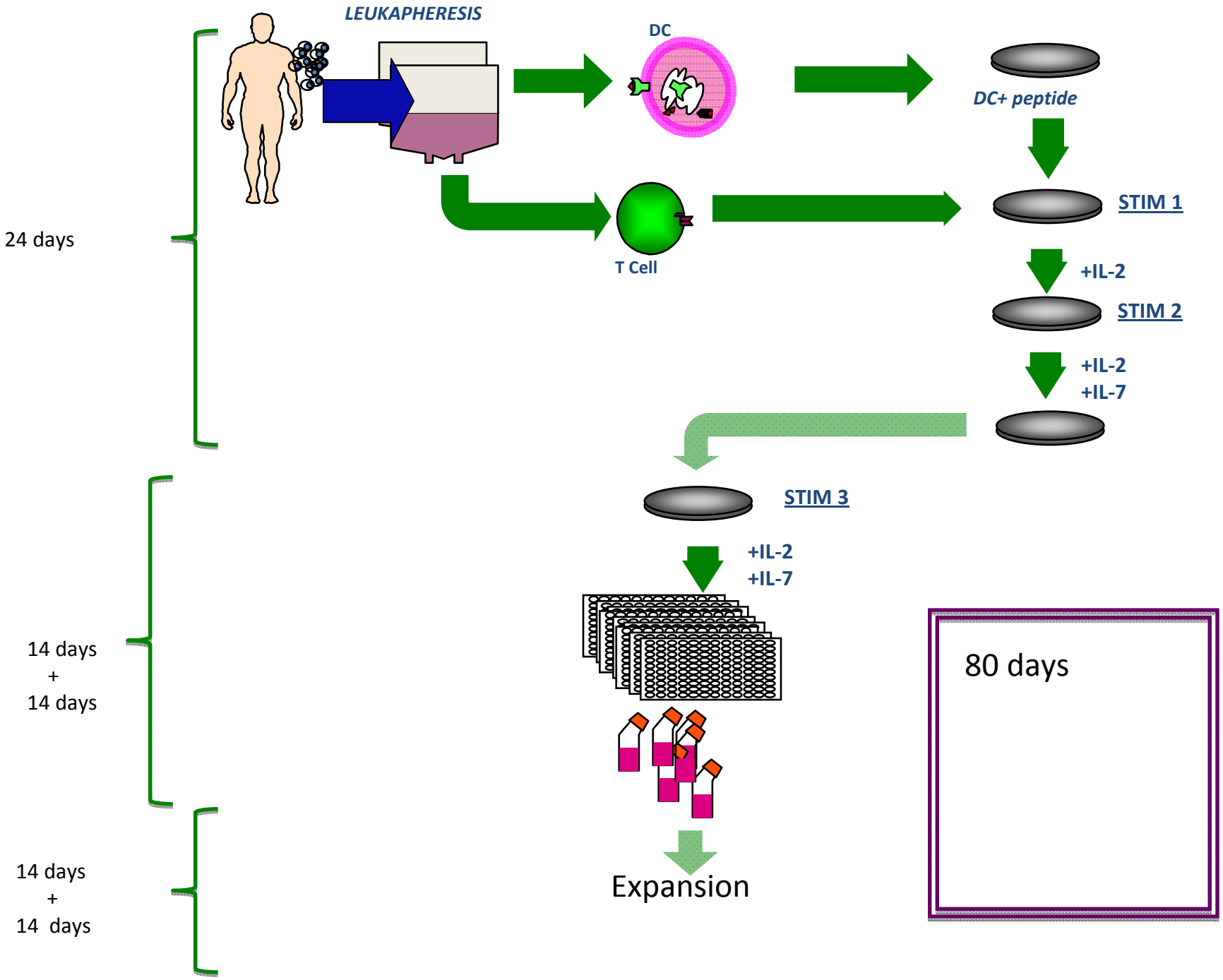
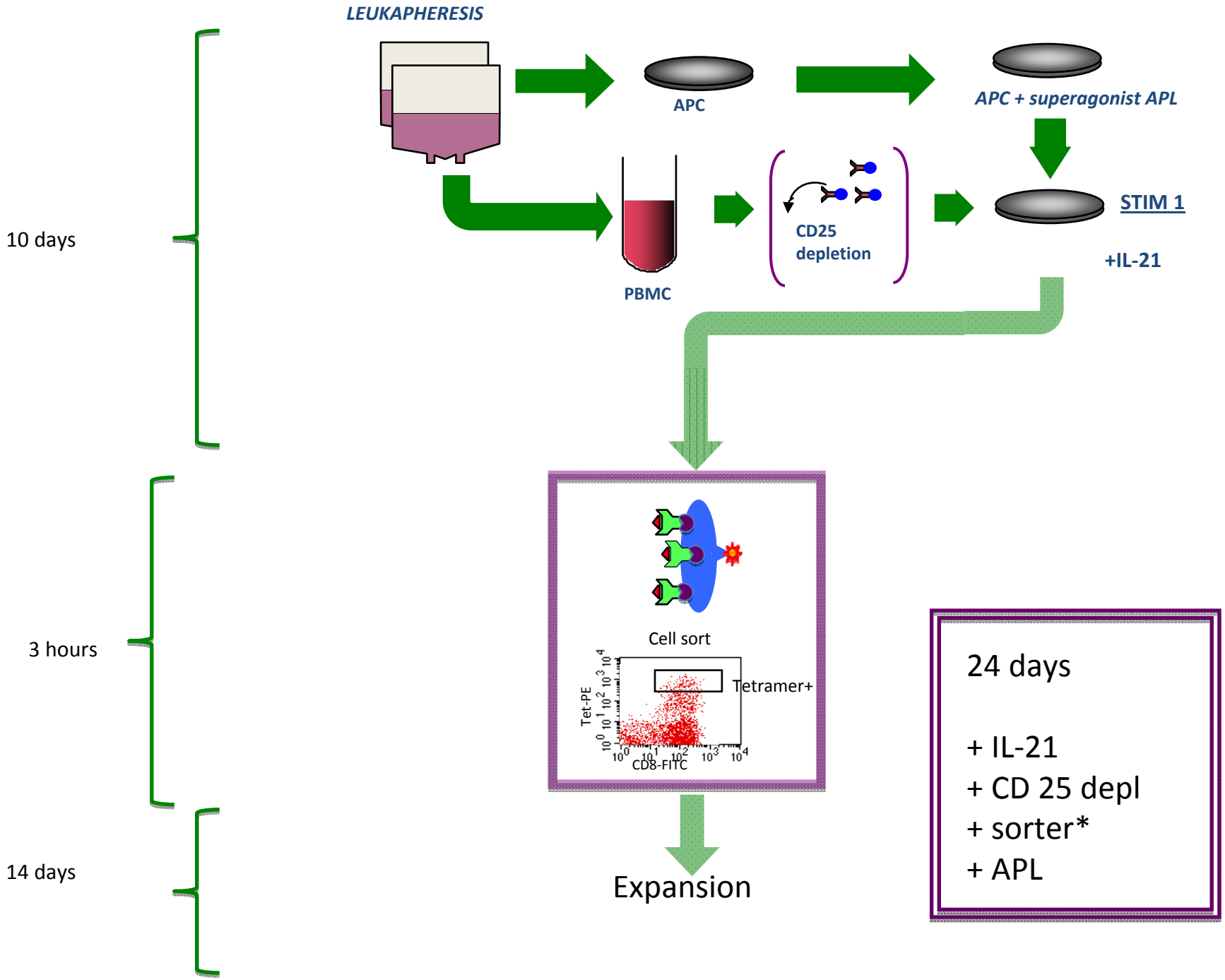

LEUKAPHERESIS
DC
DC+ peptide
T Cell
STIM 1
+IL-2
STIM 2
+IL-2
+IL-7
STIM 3
+IL-2
+IL-7
Expansion
24 days
14 days
+
14 days
14 days
+
14 days
80 days


LEUKAPHERESIS
APC
APC + superagonist APL
PBMC
CD25
depletion
STIM 1
+IL-21
10 days
3 hours
14 days
Cell sort
Tetramer+
Tet-PE
CD8-FITC
Expansion
24 days
+ IL-21
+ CD 25 depl
+ sorter*
+ APL

Immunologic monitoring

- Cellular level:
  - Epimax
  - SCBC
  - Tetramer multiplex slides
  - TCR sequencing
- Host level
  - Biopsy
  - Noninvasive imaging

Prospects for Adoptive Cellular Therapy

- Clinical indications
- Clinical setting
- Combination Therapy
- Advances in technology
  - In vitro generation of effectors
  - Combinational reagents
  - Immunologic monitoring
- Immunologic monitoring

Antigen Receptor

Which of the following is *not* true:

a. The TCR recognizes fragments of whole proteins (peptides) presented on the surface of cells by MHC molecules
b. T cells can target peptides derived from both surface and intracellular proteins
c. Chimeric antigen receptors (CARs) are fusion products of TCR alpha and beta region and cytoplasmic signaling domains
d. T cells engineered to express CARs can recognize tumor cells expressing a target surface or intracellular protein

Antigen Receptor

Which of the following is *not* true:

c. Chimeric antigen receptors (CARs) are fusion products of TCR alpha and beta region and cytoplasmic signaling domains

TIL

- Tumor infiltrating lymphocytes

a. Are comprised almost exclusively of CD8 T cells (CTL)
b. Are found only in melanoma tumor samples
c. Can only be expanded in vitro using high-dose IL-2
d. Are a source of antigen-specific T cell

TIL

- Tumor infiltrating lymphocytes

d. Are a source of antigen-specific T cell

CD4 T cells

- The following statement regarding CD4 T cells is not true:

a. Recognize peptide presented by Class I MHC

b. Can kill tumor cells directly

c. Can recruit other nonspecific effector cells to the tumor site

d. Can be regulatory / suppressor T cells

CD4 T cells

- The following statement regarding CD4 T cells is not true:

a. Recognize peptide presented by Class I MHC

Peptide-MHC multimers

- Which are the following statements is not true:
- Peptide-MHC multimers

a. Can be used to identify antigen-specific CD8 T cells
b. Can be used to sort and isolate rare antigen-specific T cells
c. Can be used for immunohistochemistry staining
d. Cannot be used to identify antigen-specific CD4 T cells

Peptide-MHC multimers

- Which are the following statements is not true:
- Peptide-MHC multimers

d. Cannot be used to identify antigen-specific CD4 T cells

Current Events

- The artist known as _____ is famous for popularizing the ‘Gangnam-style’ of dancing:

a. Jerry Garcia

b. I 

c. ICE-T

d. PSY

Current Events

- The artist known as _____ is famous for popularizing the ‘Gangnam-style’ of dancing:

d. PSY


2417
2128
3730