Adoptive Cellular Therapy

SITC Primer

2013

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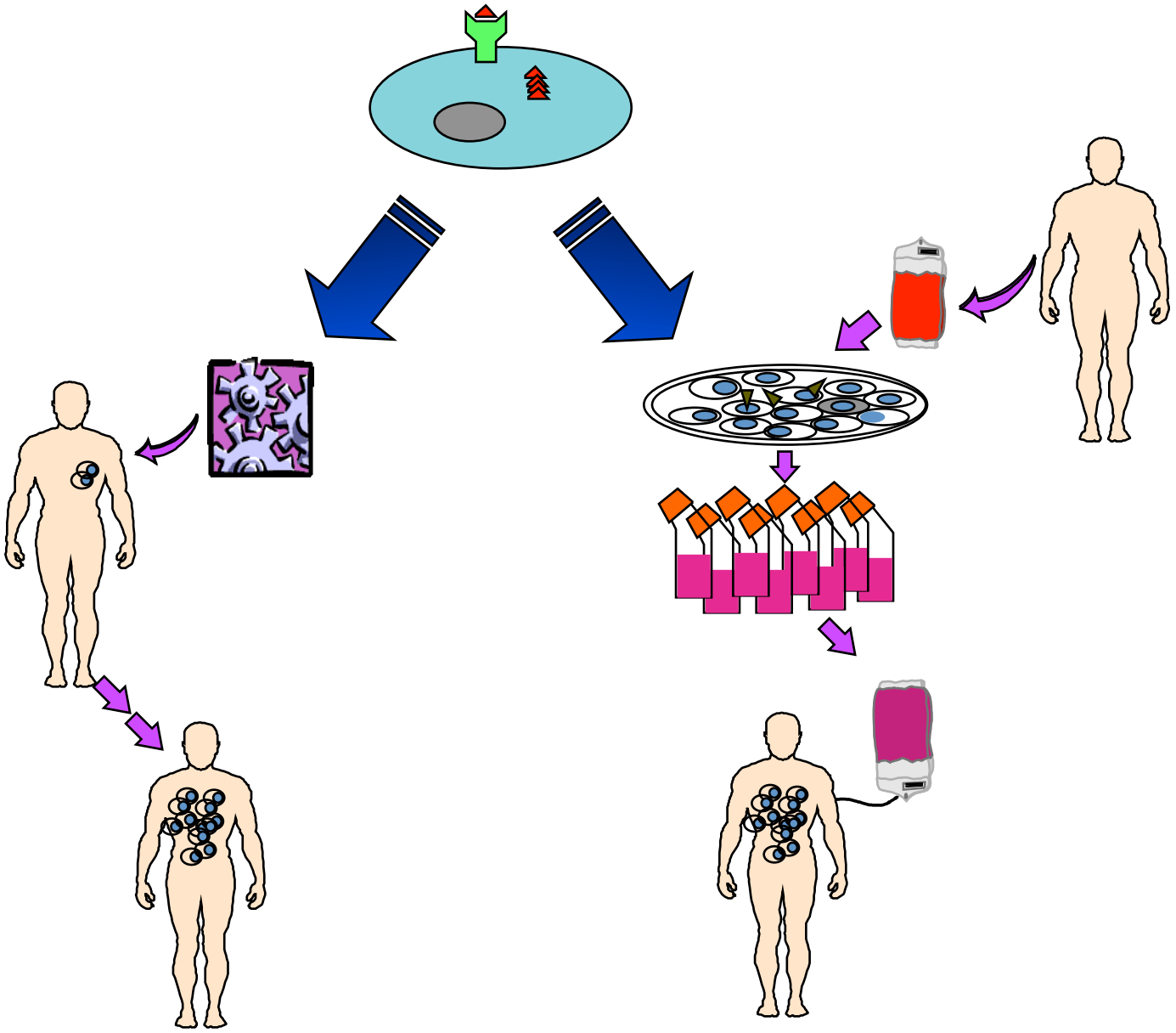
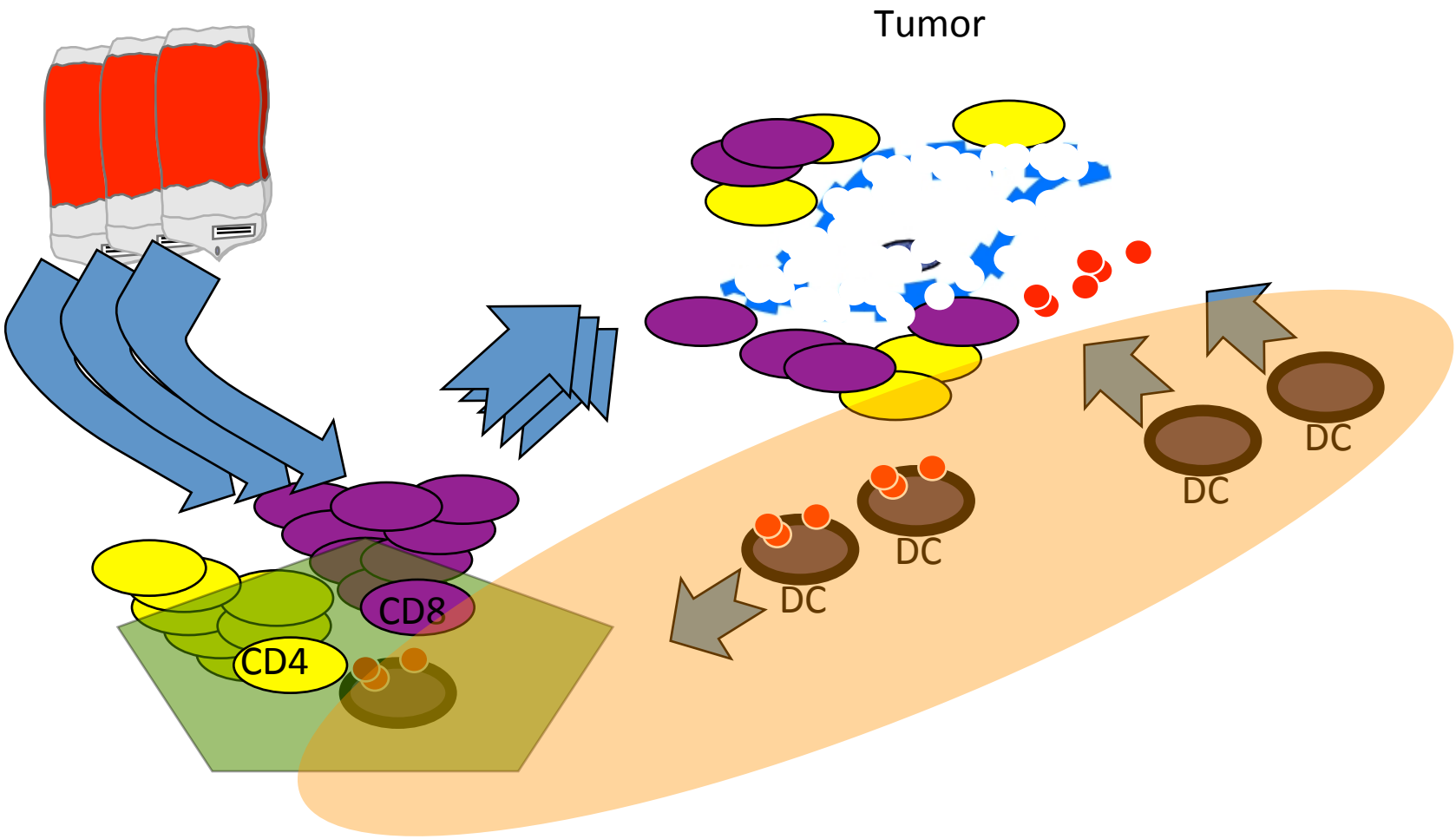

Vaccine Therapy
Adoptive Therapy

Adoptive T Cell Therapy



- Effectors:
  - TIL, CAR/TCR, Endogenous
  - Clinical results

- Extrinsic Factors
  - Immunomodulation of Host / TME
  - Combination

Choice of Effectors

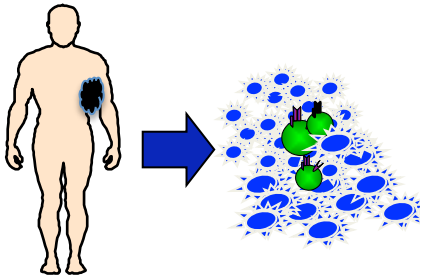
TIL	Transferred Receptors CAR/TCR	Endogenous Receptor

Choice of Effectors

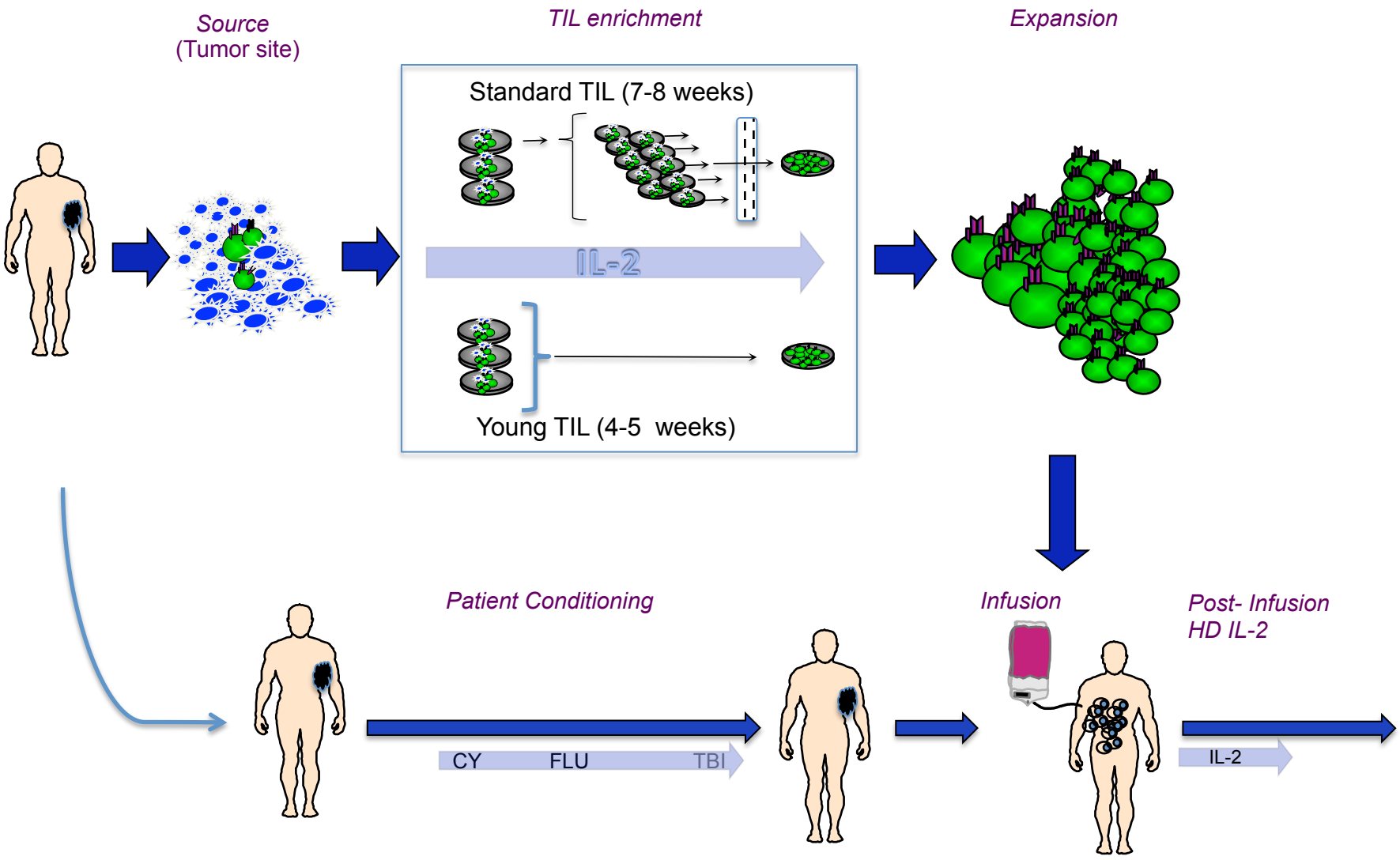
TIL	Transferred Receptors CAR/TCR	Endogenous Receptor

Tumor-Infiltrating Lymphocyte (TIL) Therapy

Source
(Tumor site)



Tumor-Infiltrating Lymphocyte (TIL) Therapy



Tumor Infiltrating Lymphocyte

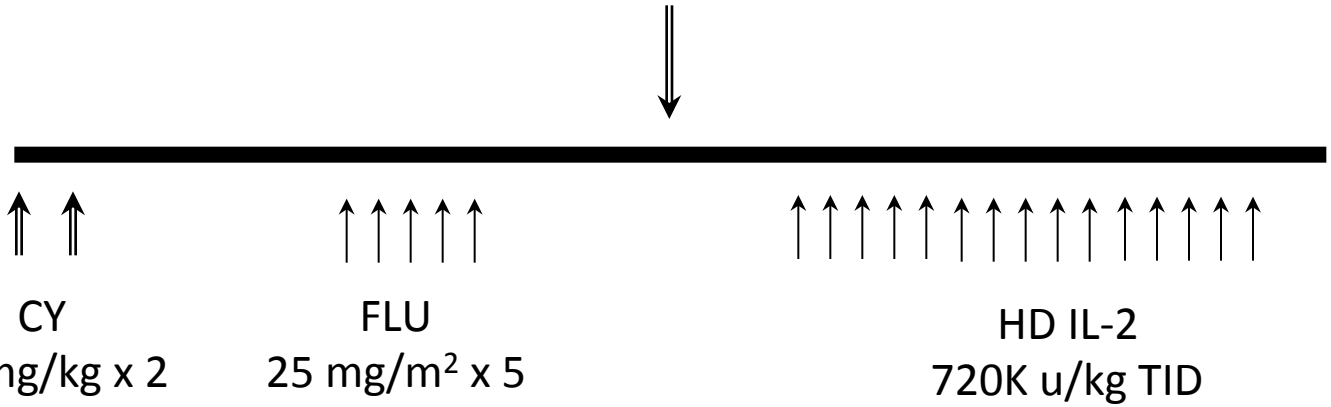
TIL	Transferred Receptors CAR/TCR	Endogenous Receptor
Requires tumor **HD IL-2 dependence**		
Least labor intensive		

Tumor Infiltrating Lymphocyte

Adoptive Therapy following
Non-myeloablative Lymphodepletion

Study Design

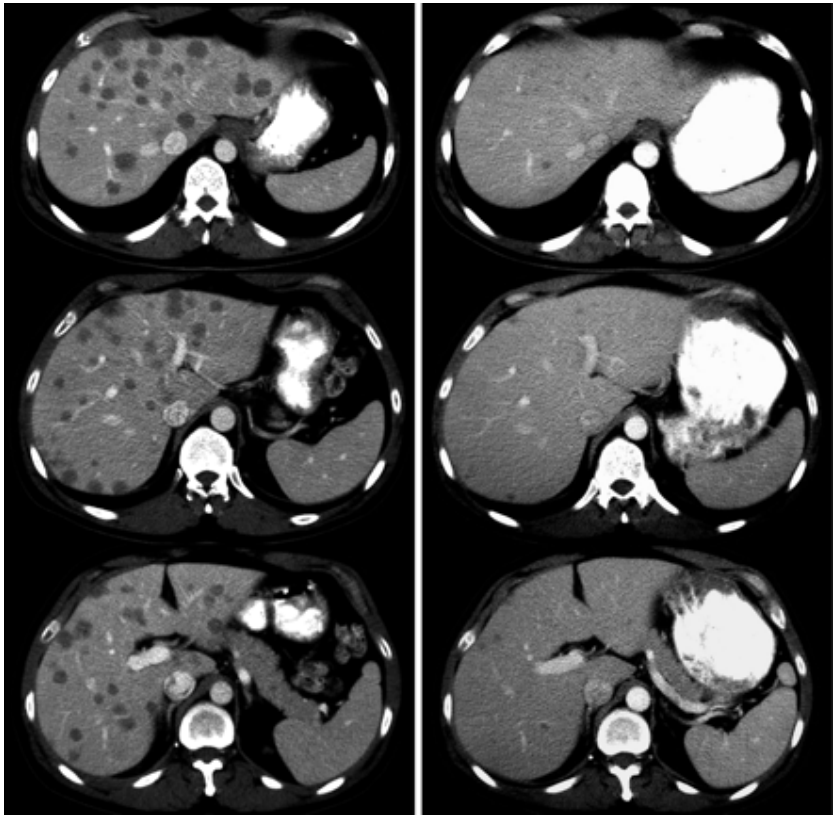
- Patients with metastatic melanoma
- Treated at time of progression, refractory disease
- TIL expanded in vitro to > 10^{10} cells



Dudley et al, Science 2002

Tumor Infiltrating Lymphocyte

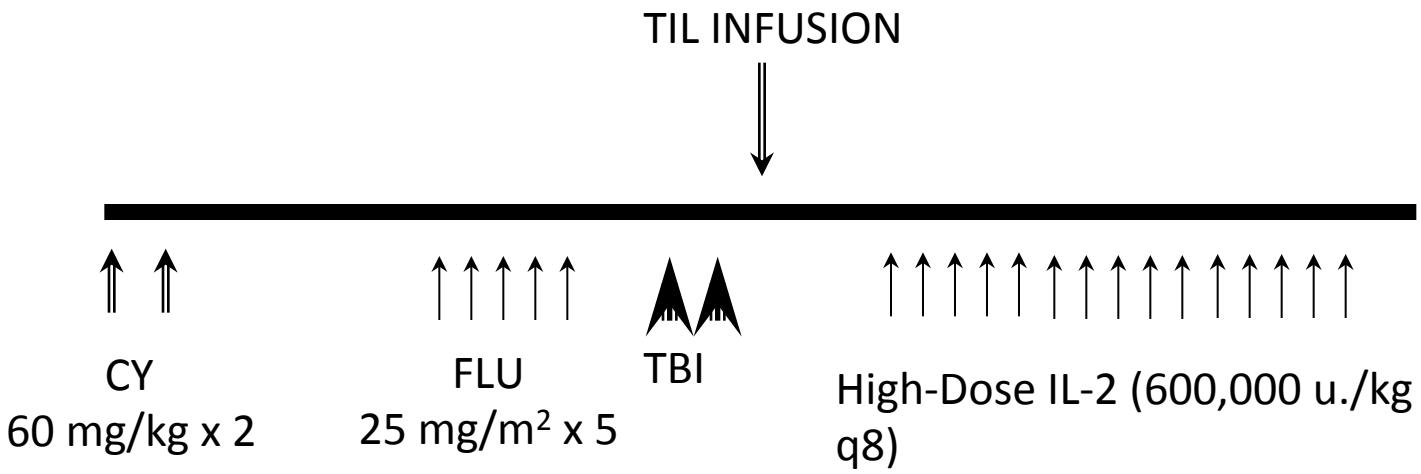
Pre- Post-



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

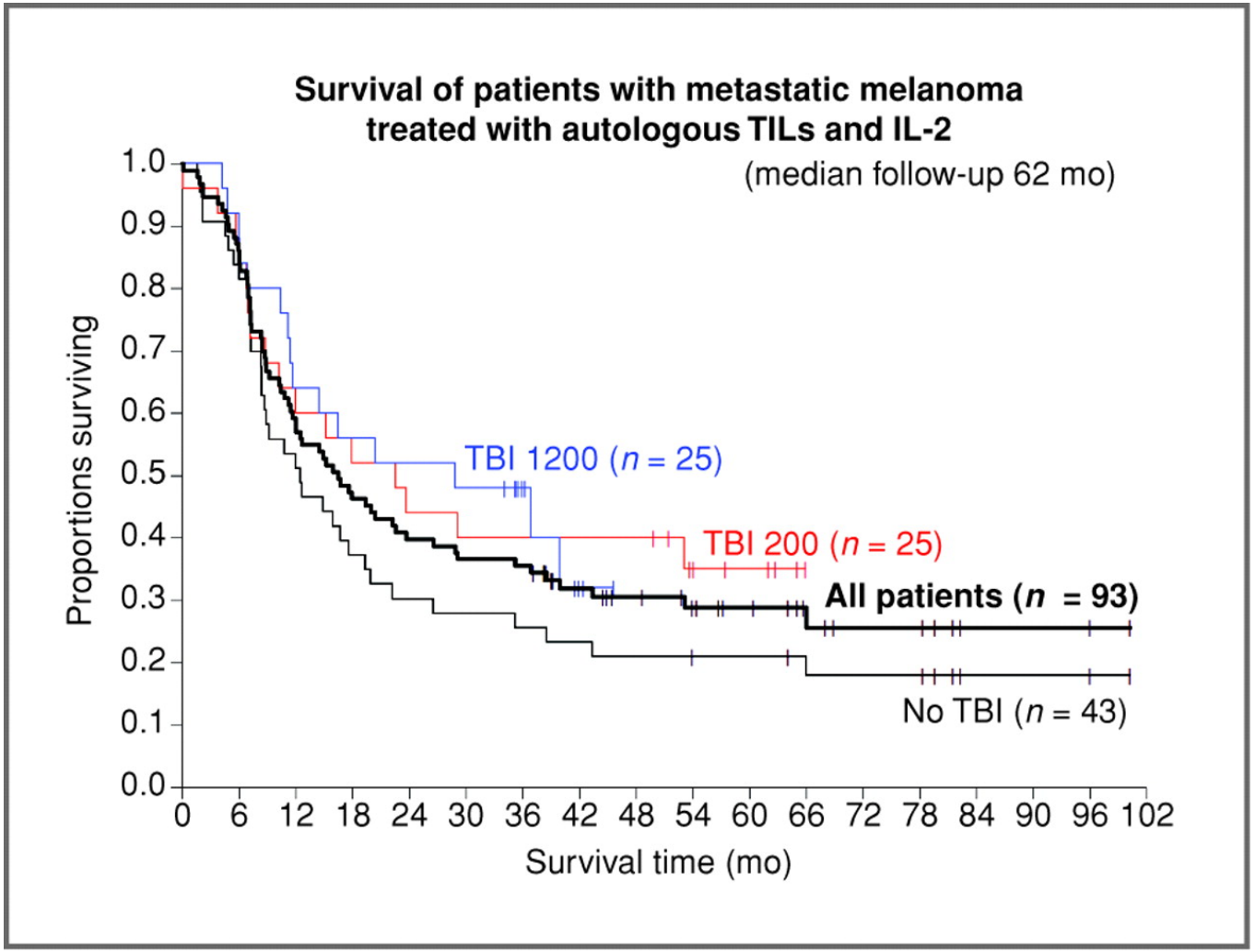


Tumor Infiltrating Lymphocyte

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

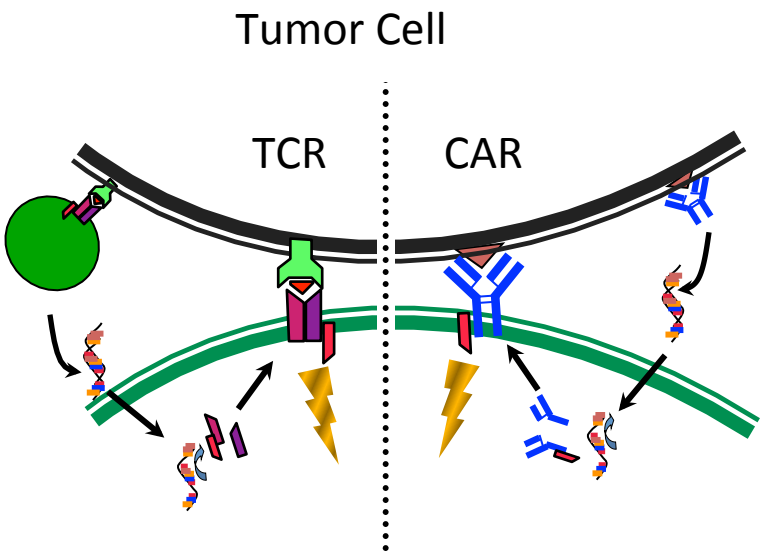
TIL Therapy

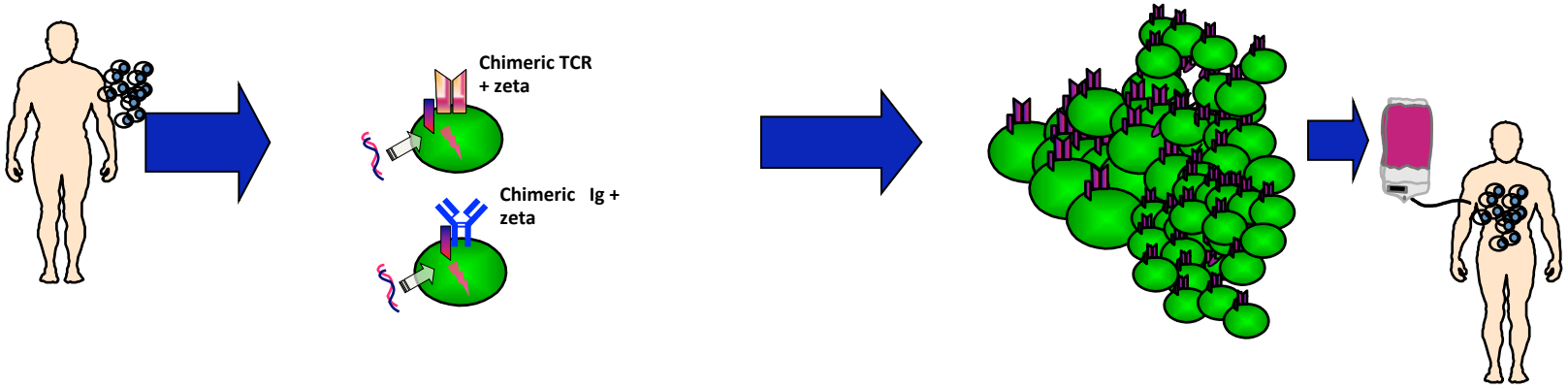
- Significant responses
- Patient eligibility
- Facilities available
- 2nd and 3rd generation TIL
  - Gene-modification
  - Selection

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**	

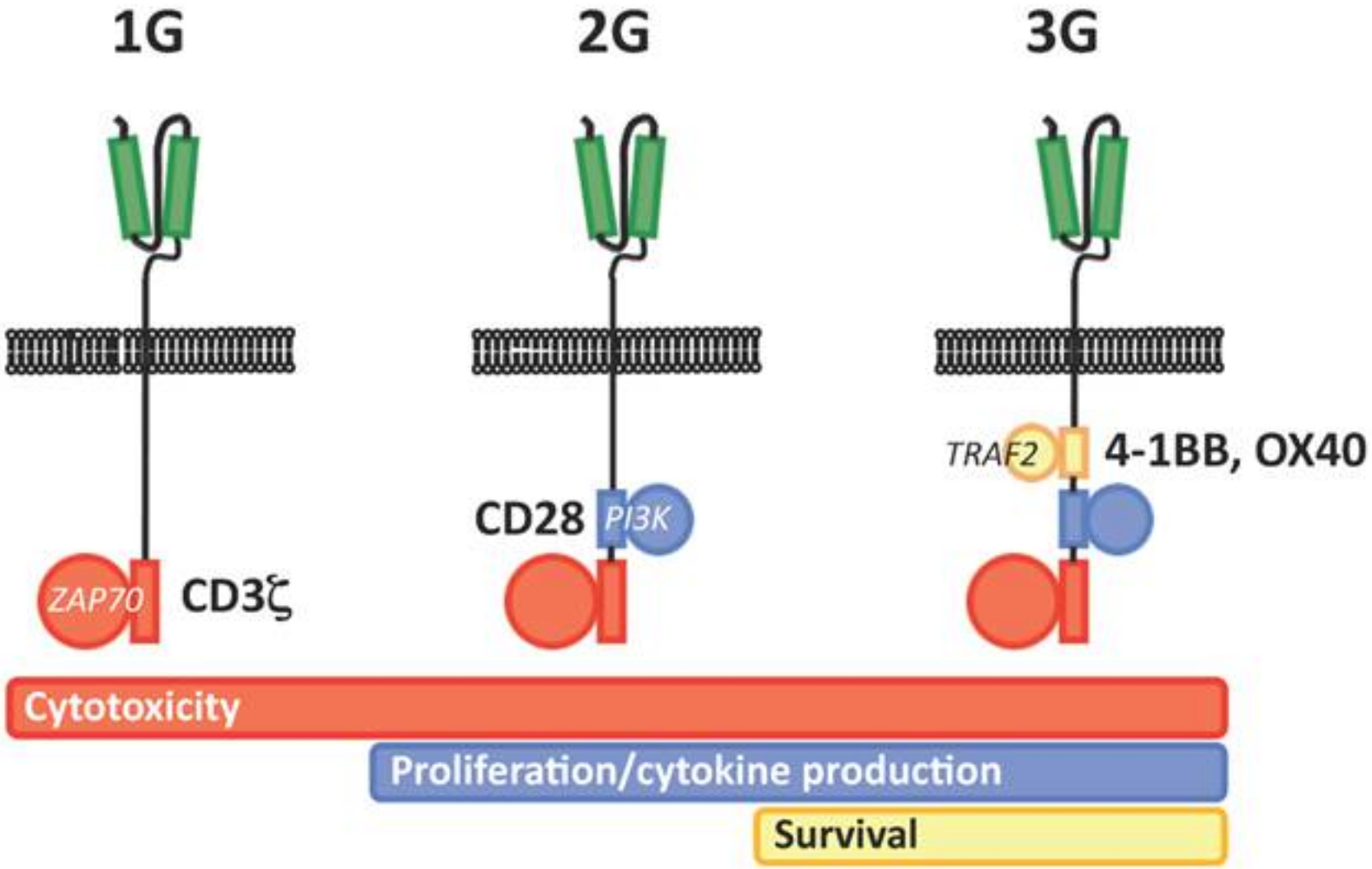
Transferred Receptor: TCR / CAR





Receptor Transfer

T Cell Expansion & Infusion



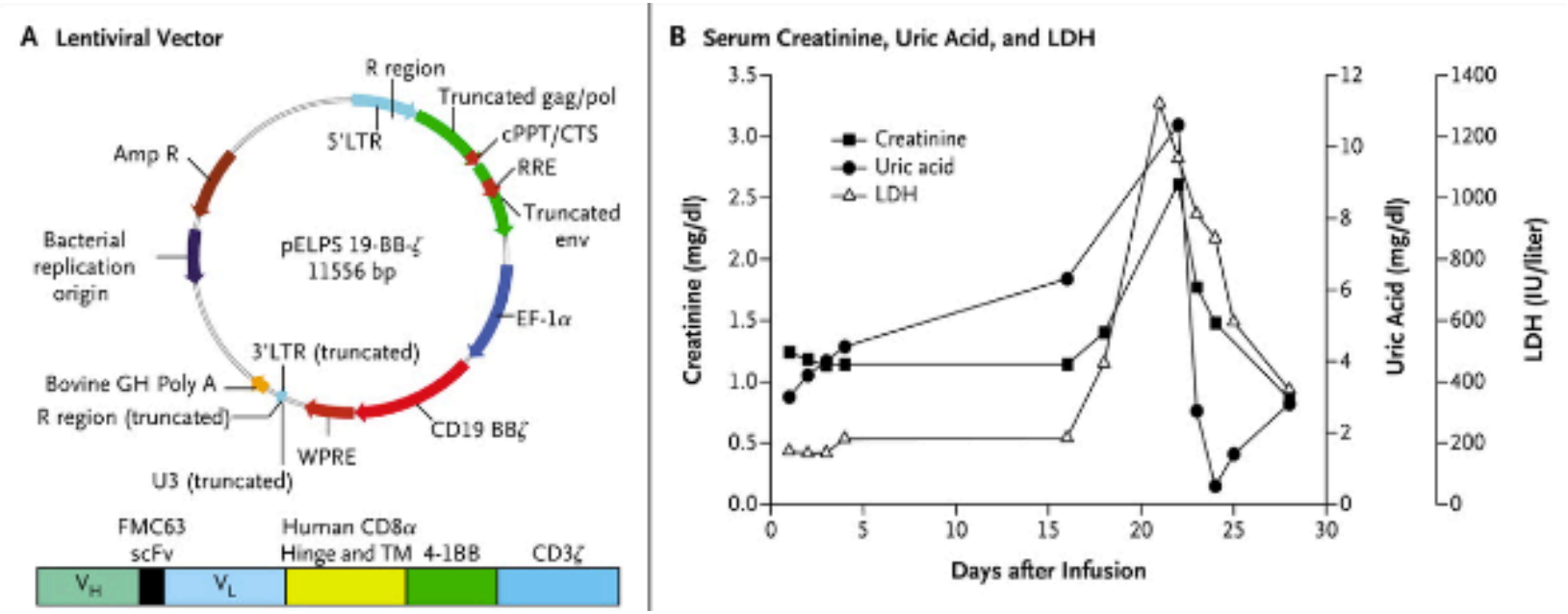
Casucci et al, J Cancer 2011; 2:378-382

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

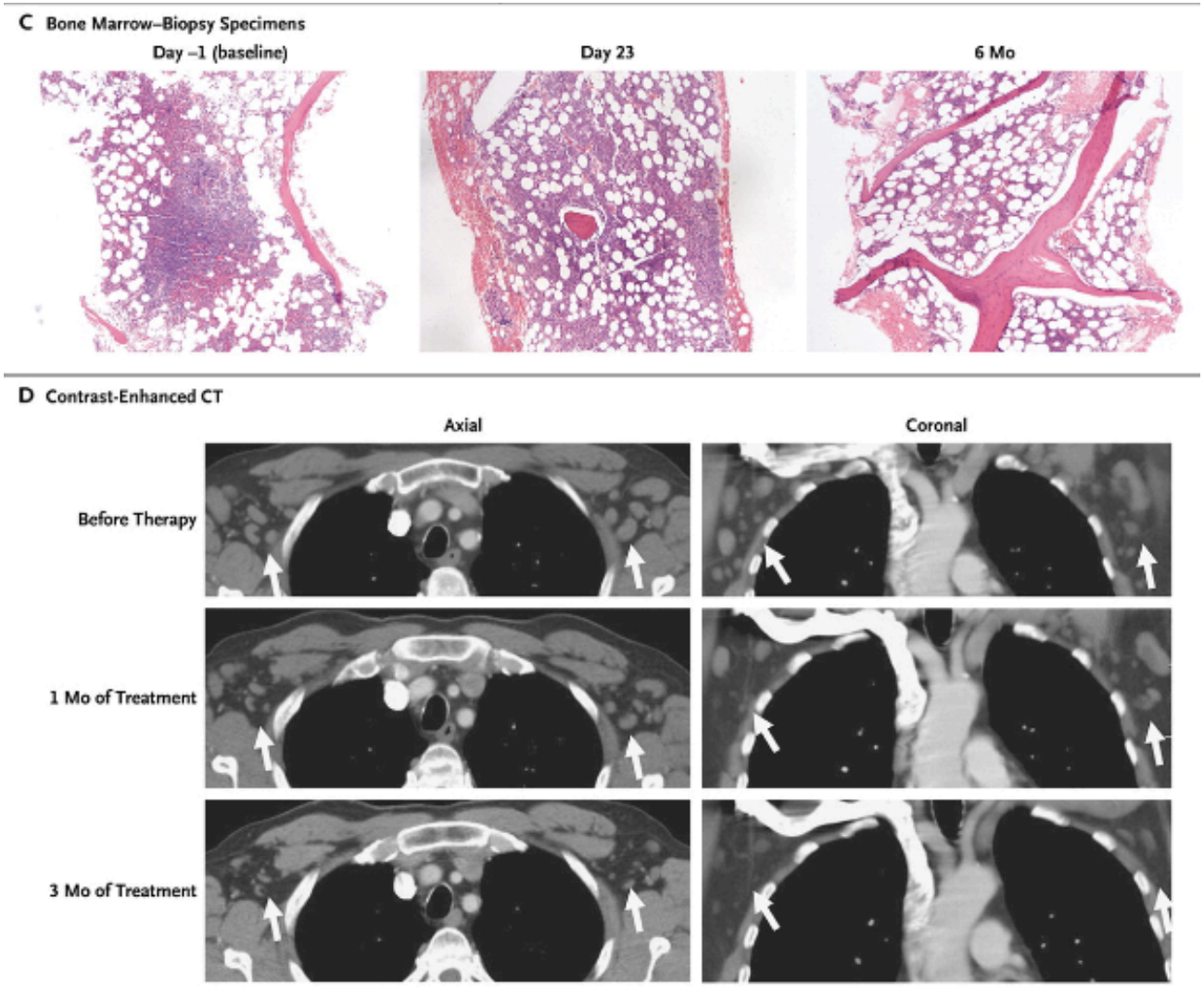
T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia
Michael Kalos, Bruce Levine, David Porter, Sharyn Katz, Stephan Grupp, Adam Bagg, Carl H. June
Sci Transl Med 10 August 2011: Vol. 3, Issue 95, p. 95ra73

Transferred Receptor: TCR / CAR



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

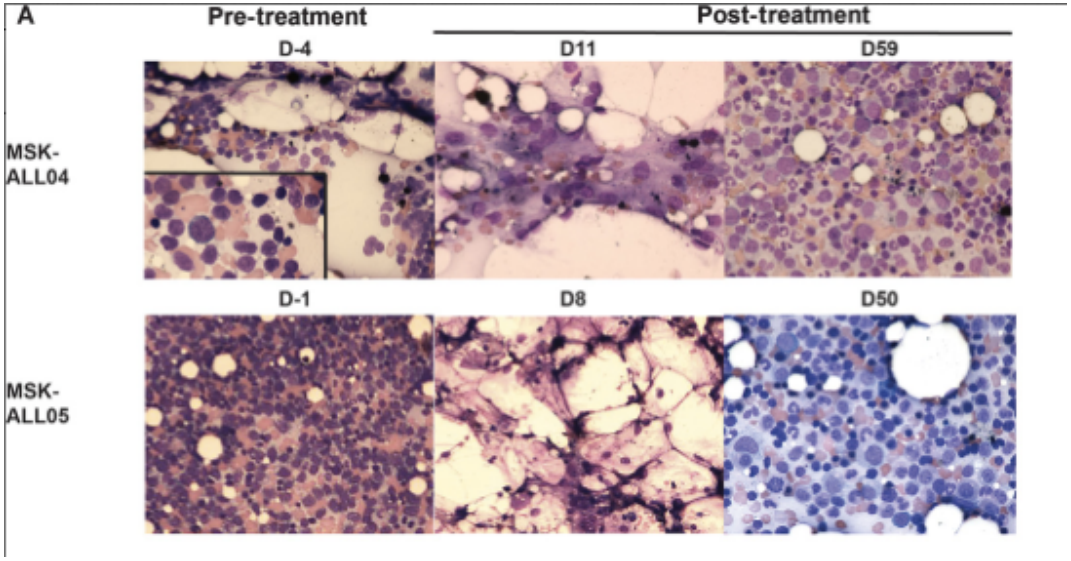
Transferred Receptor: TCR / CAR

Anti-CD19-CD28z

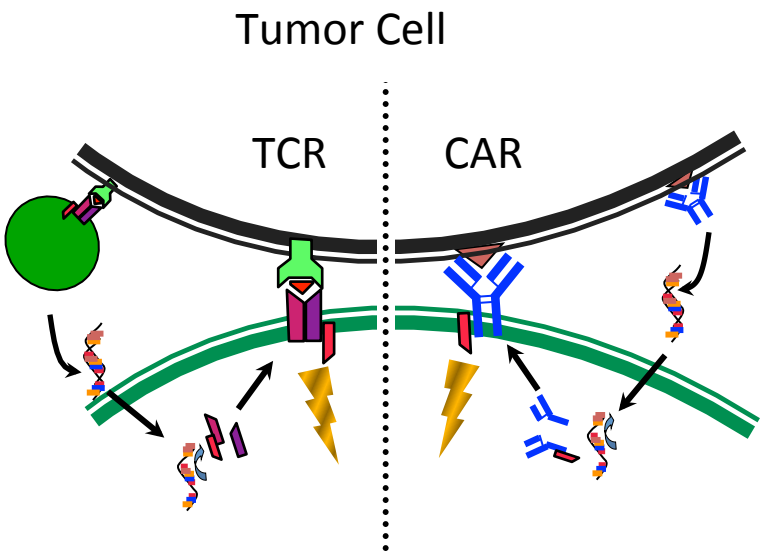
Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias (CLL).
Blood. 2011 Nov 3;118(18):4817-28. Brentjens RJ…Sadelain M

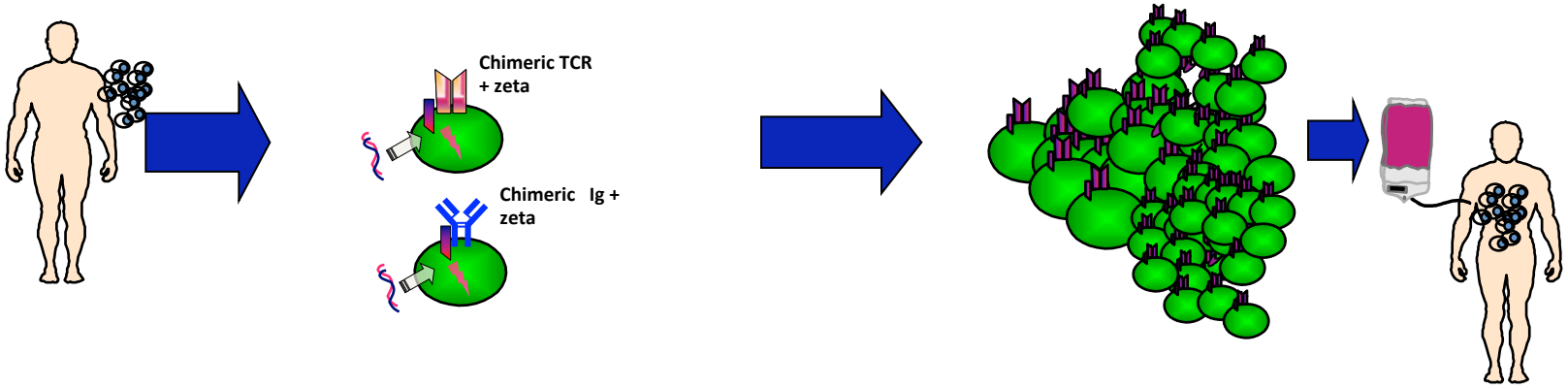
CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med. 2013 Mar 20;5(177):177. Renier J. Brentjens et al.

5 of 5 patients with ALL (2 Ph+) → MRD-



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

"The Basic Principles of Chimeric Antigen Receptor Design" Michel Sadelain , Renier Brentjens , and Isabelle Rivière. Cancer Discov; 3(4); 388–98.

Transferred Receptor: TCR / CAR

Molecular Construct Issues

- CAR/TCR: affinity
  - Phage display, mutations
  - Safety, cross-reactivity
- TCR: pairing
  - Disulfide, murine, zipper
- Transfection efficiency
  - Lentiviral, SB transposon
- Cell type
- Immunogenicity

Transferred Receptor: TCR / CAR

Clinical Issues

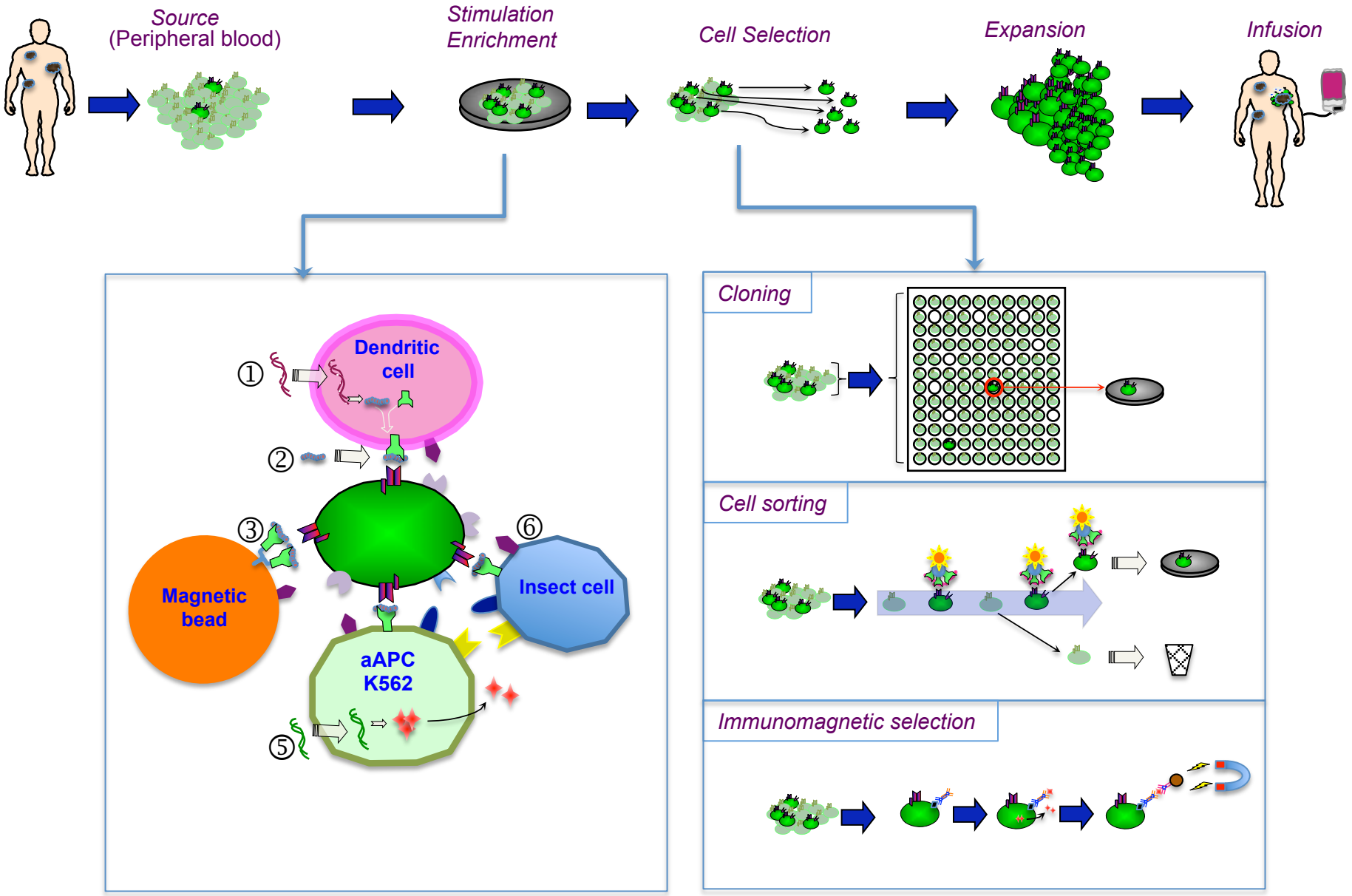
- Cytokine release syndrome toxicity
- On-target Toxicities

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

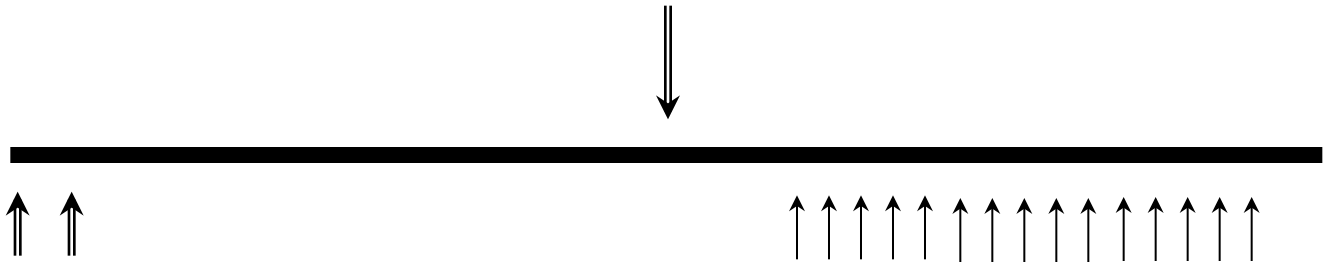
Choice of Effectors

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

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

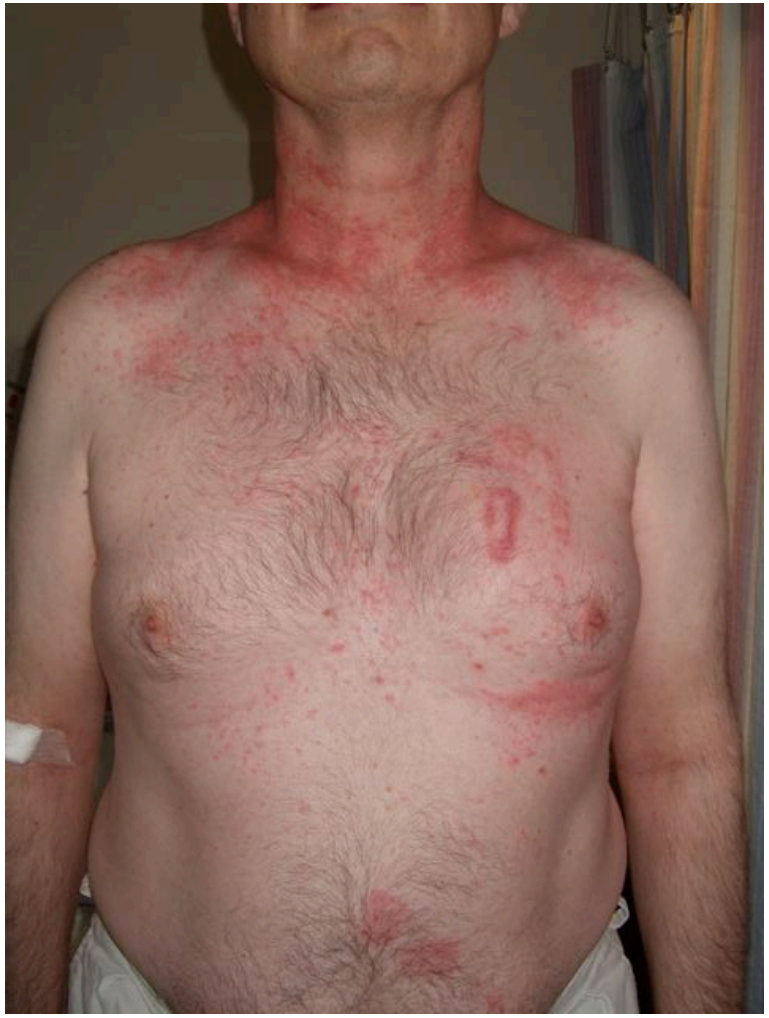
Aude G. Chapuis[a], John A. Thompson[b], Kim A. Margolin[b], Rebecca Rodmyre[a], Ivy P. Lai[a], Kaye Dowdy[a], Erik A. Farrar[a], Shailender Bhatia[b], Daniel E. Sabath[c], Jianhong Cao[a], Yongqing Li[a], and Cassian Yee[a,1]

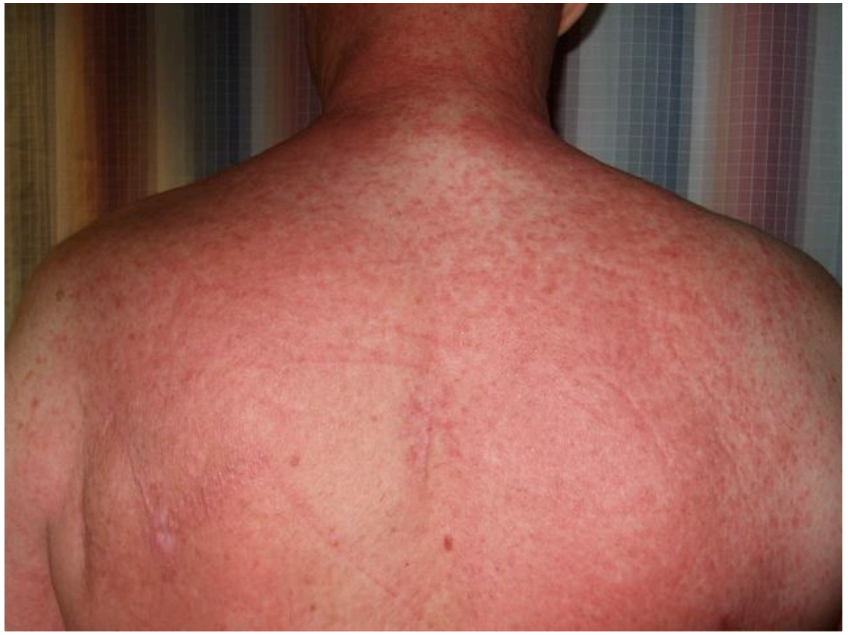
[a]Program in Immunology, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; [b]General Oncology and Hematology, Seattle Cancer Care Alliance and University of Washington, Seattle, WA 98109; and [c]Department of Laboratory Medicine, University of Washington, Seattle, WA 98195

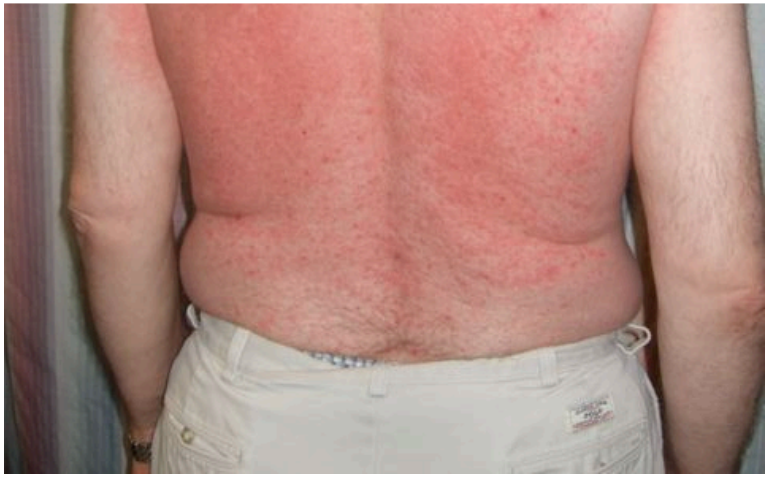
Chapuis A. et al, PNAS. March 2012

Endogenous Receptor

On-target toxicity



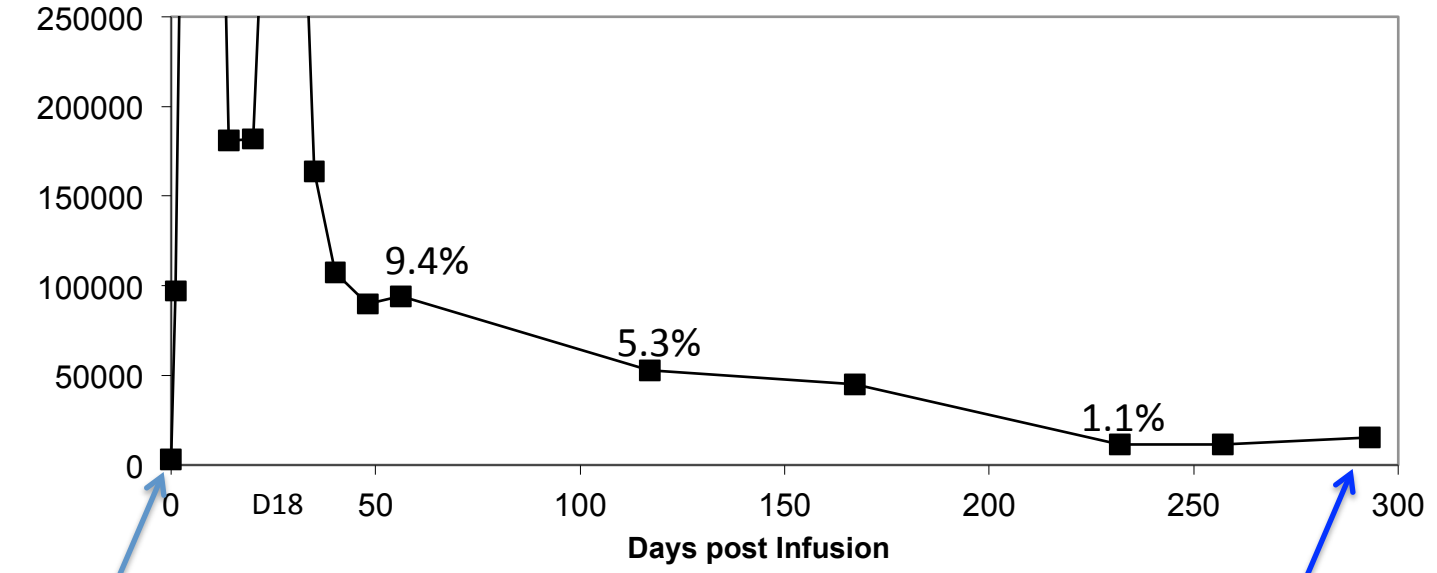




Endogenous Receptor

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

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)

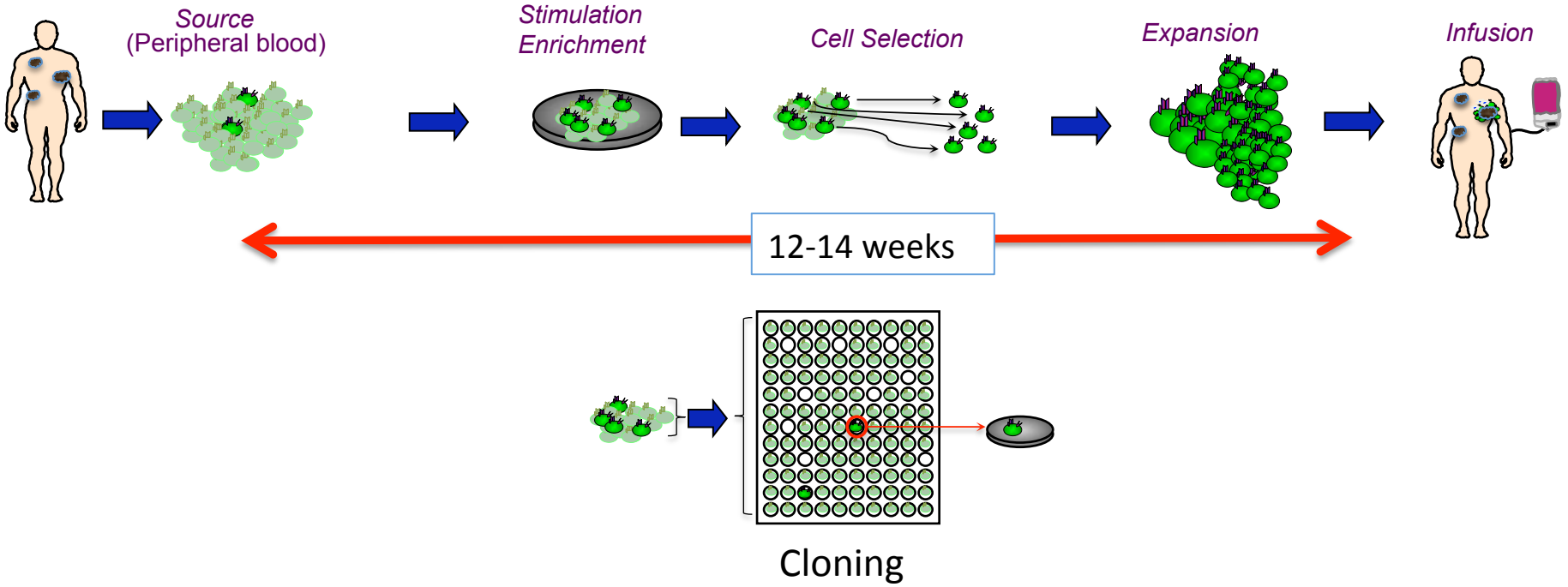
Endogenous Receptor

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+

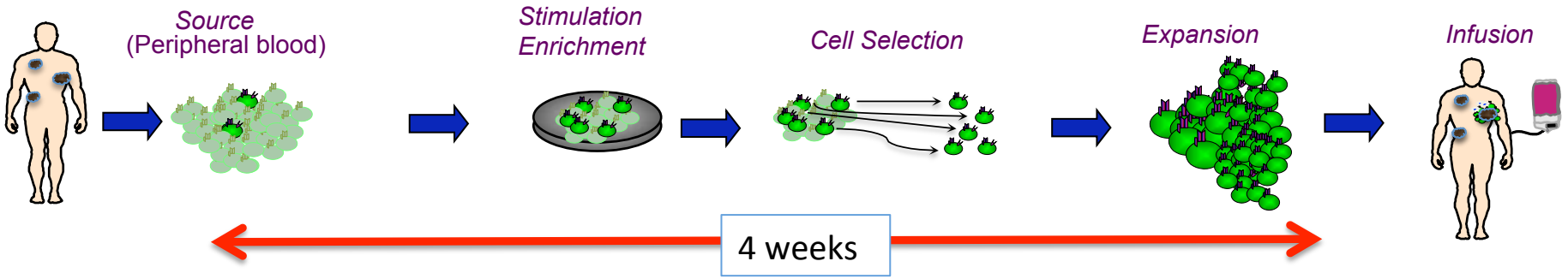
Endogenous Receptor

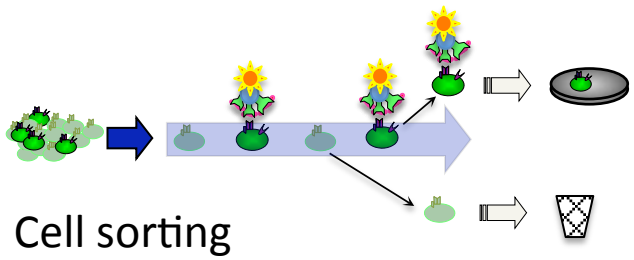
- Effective, Relatively low toxicity
- Clinical Responses (RECIST)
- Longterm persistence
- Reversion to Memory (?)
- Effector Cell type?
- Time to generation of Effector Cells

Endogenous Receptor

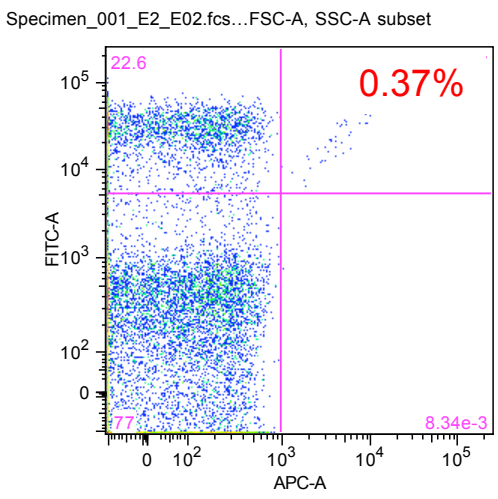


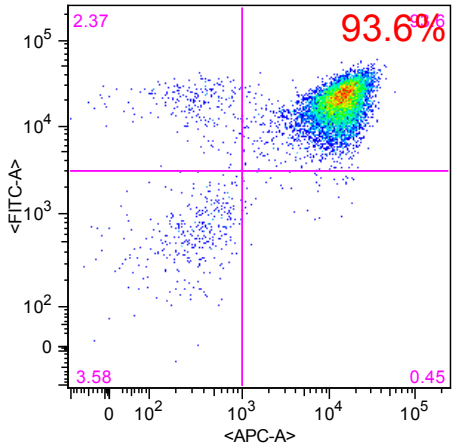
Endogenous Receptor





Clinical Grade pMHC-multimer-based Sorting





The bigger picture…

- Effectors:
  - TIL, CAR/TCR, Endogenous
  - Clinical results

- Extrinsic Factors
  - Immunomodulation of Host / TME
  - Combination