Tumor-Infiltrating Lymphocytes and Adoptive Immunotherapy

Mark B. Faries, MD, FACS

Professor of Surgery

Chief, Donald L. Morton Melanoma Research Program

Program Director, JWCI Complex General Surgical Oncology Fellowship

Director, Therapeutic Immunology

JOHN WAYNE CANCER INSTITUTE at Saint John's Health Center

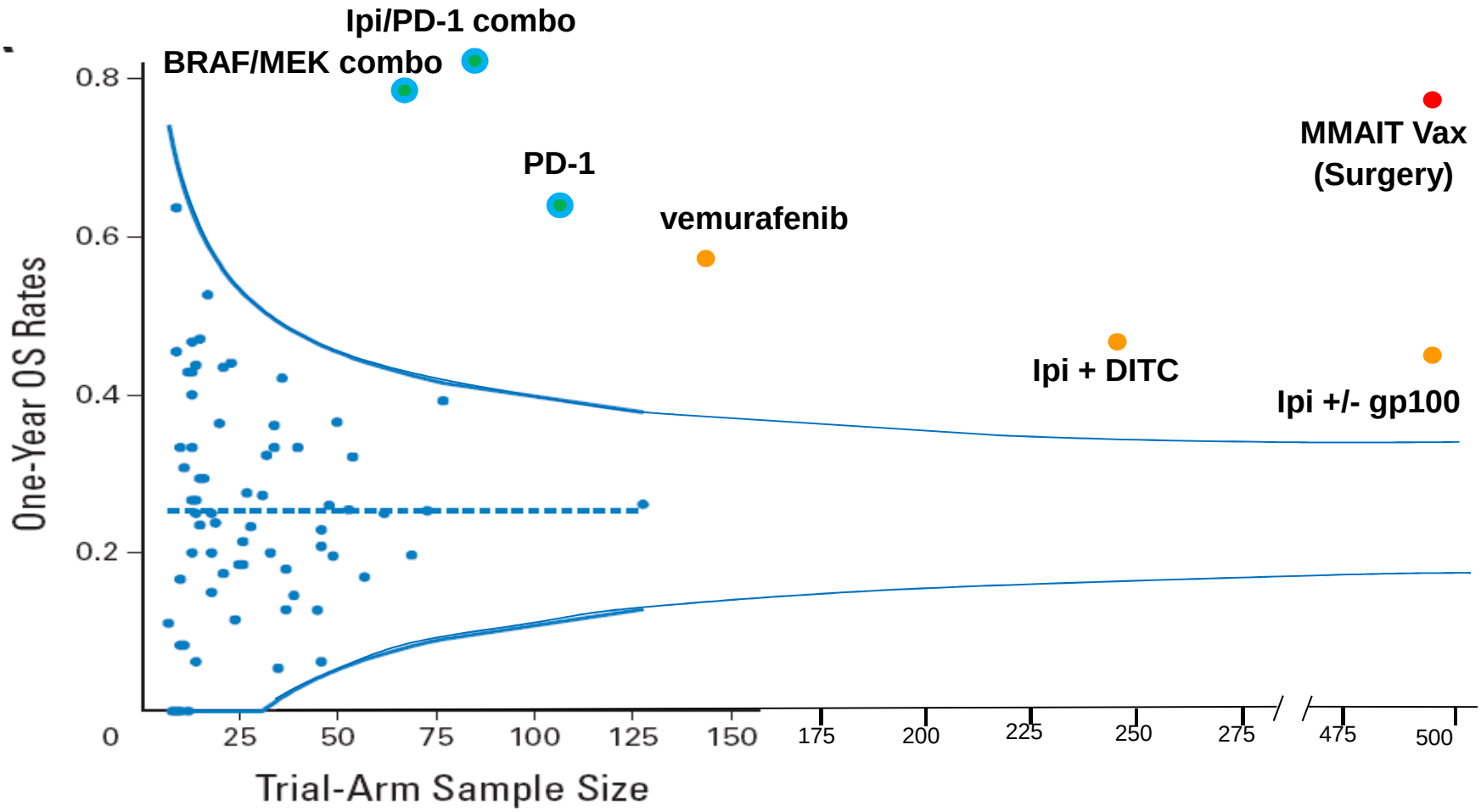
Saint John's Health Center

PROVIDENCE Health & Services

Outline

- T-cells within the immune system and cancer
- Therapeutic use of T-cells
- Adoptive Immunotherapy
  - Straight-up
  - Genetically Modified T cells
  - Bispecifics

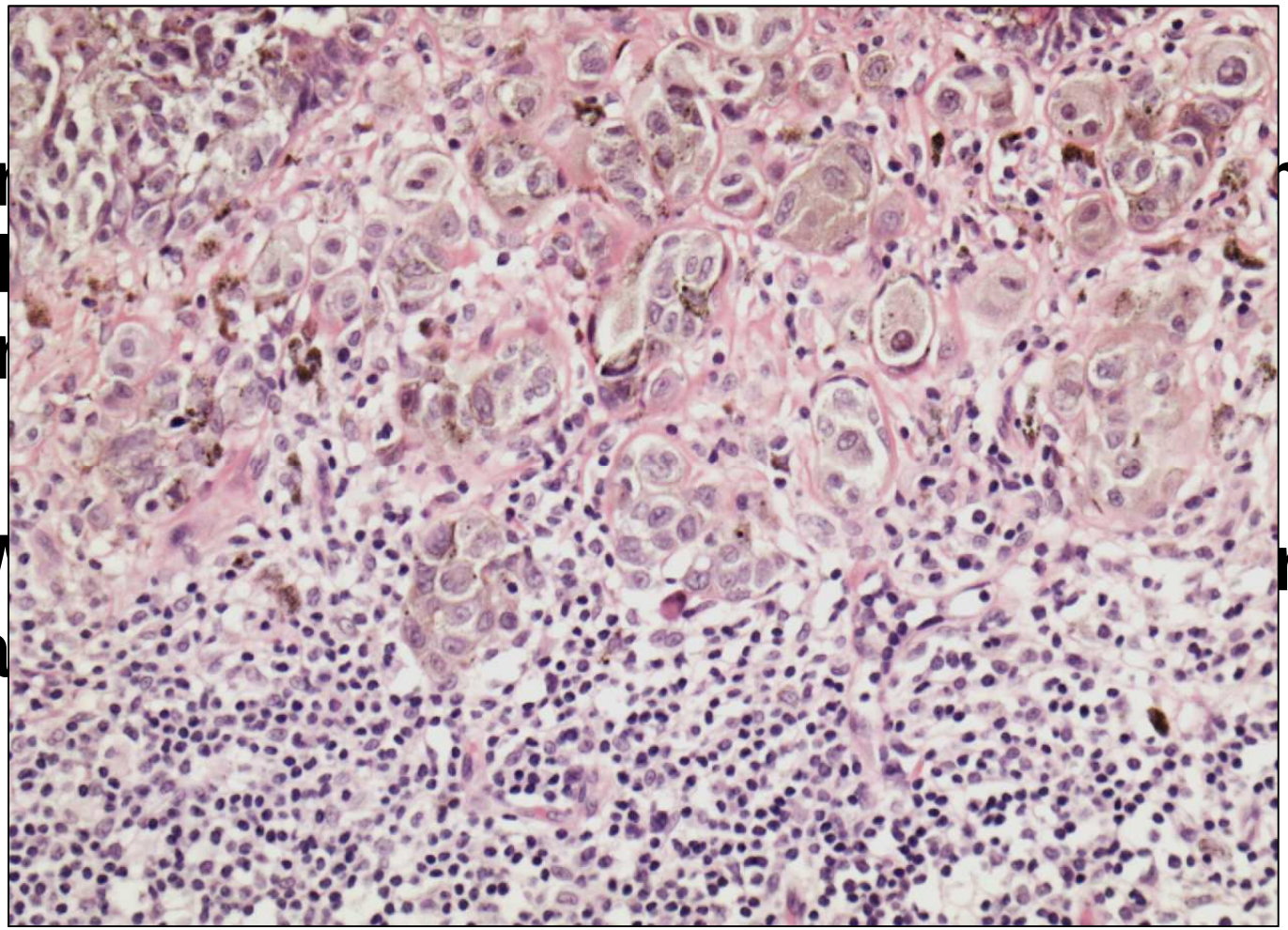
Trial Patient Outcomes Over the Years



Korn et al. *J Clin Oncol*. Feb 1 2008, 527-34.

Tumor-Infiltrating Lymphocytes

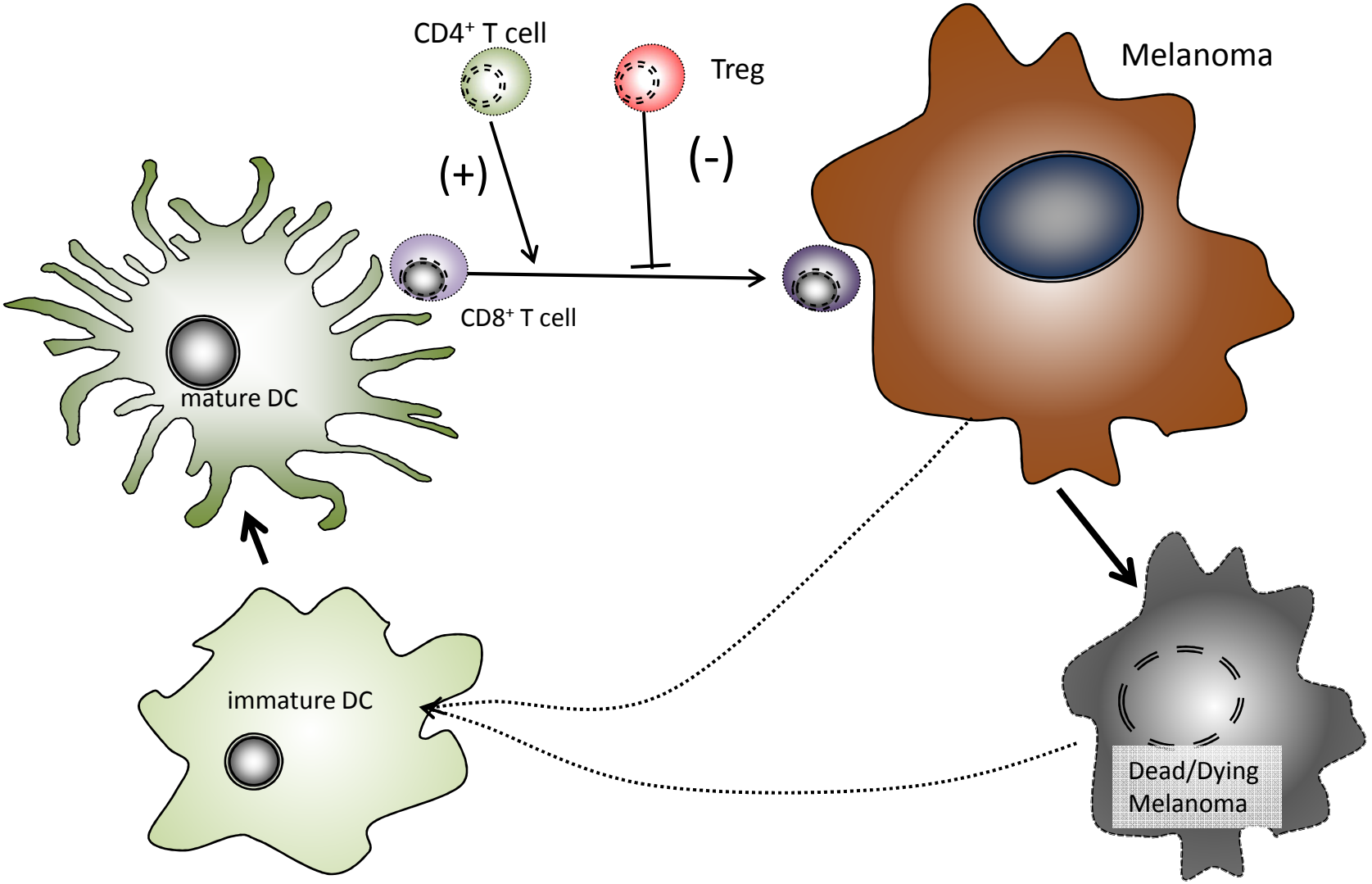
- **Natural immune recognition of melanoma is common**



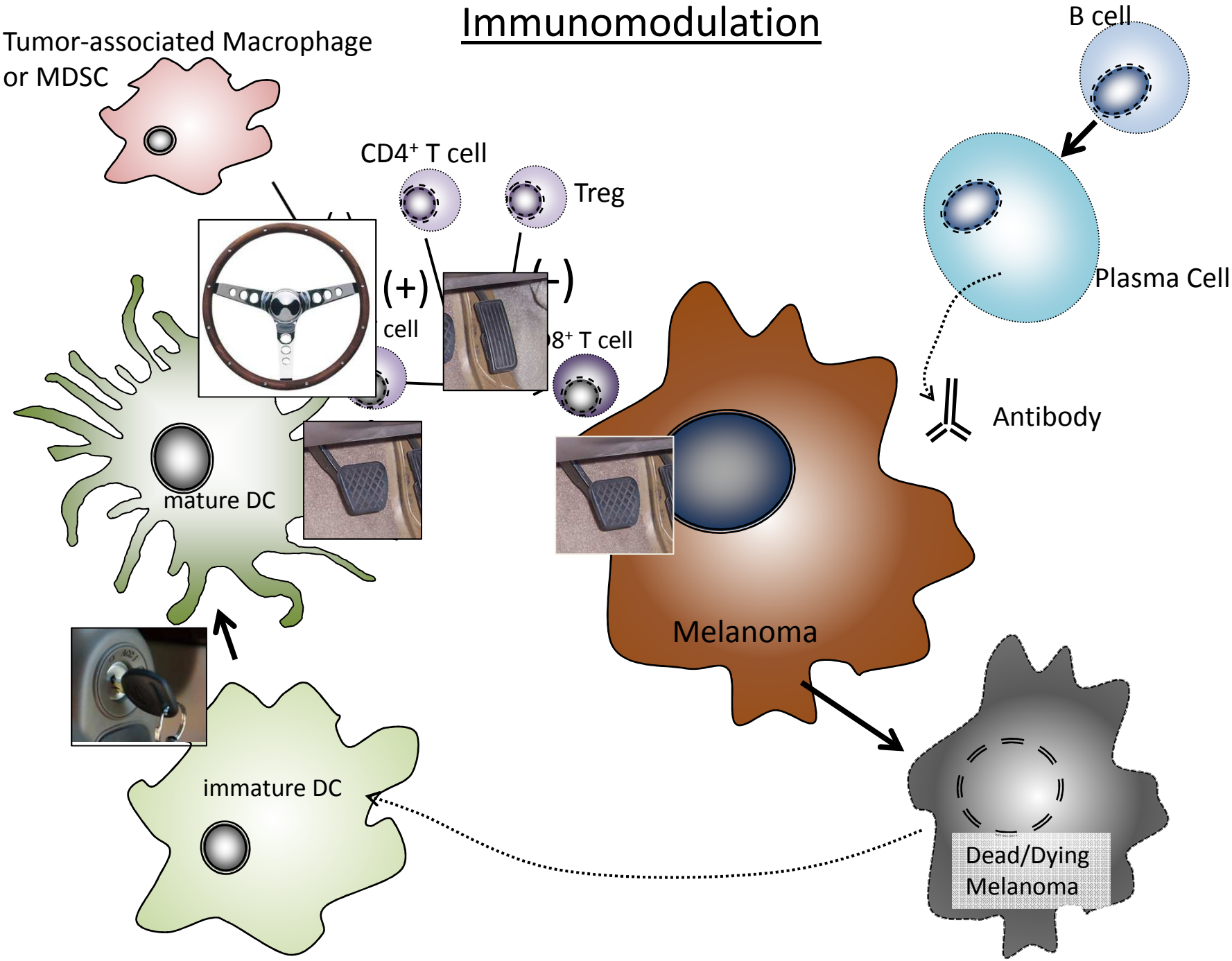
- **In**
- **V**

na,
t
i
ne
a

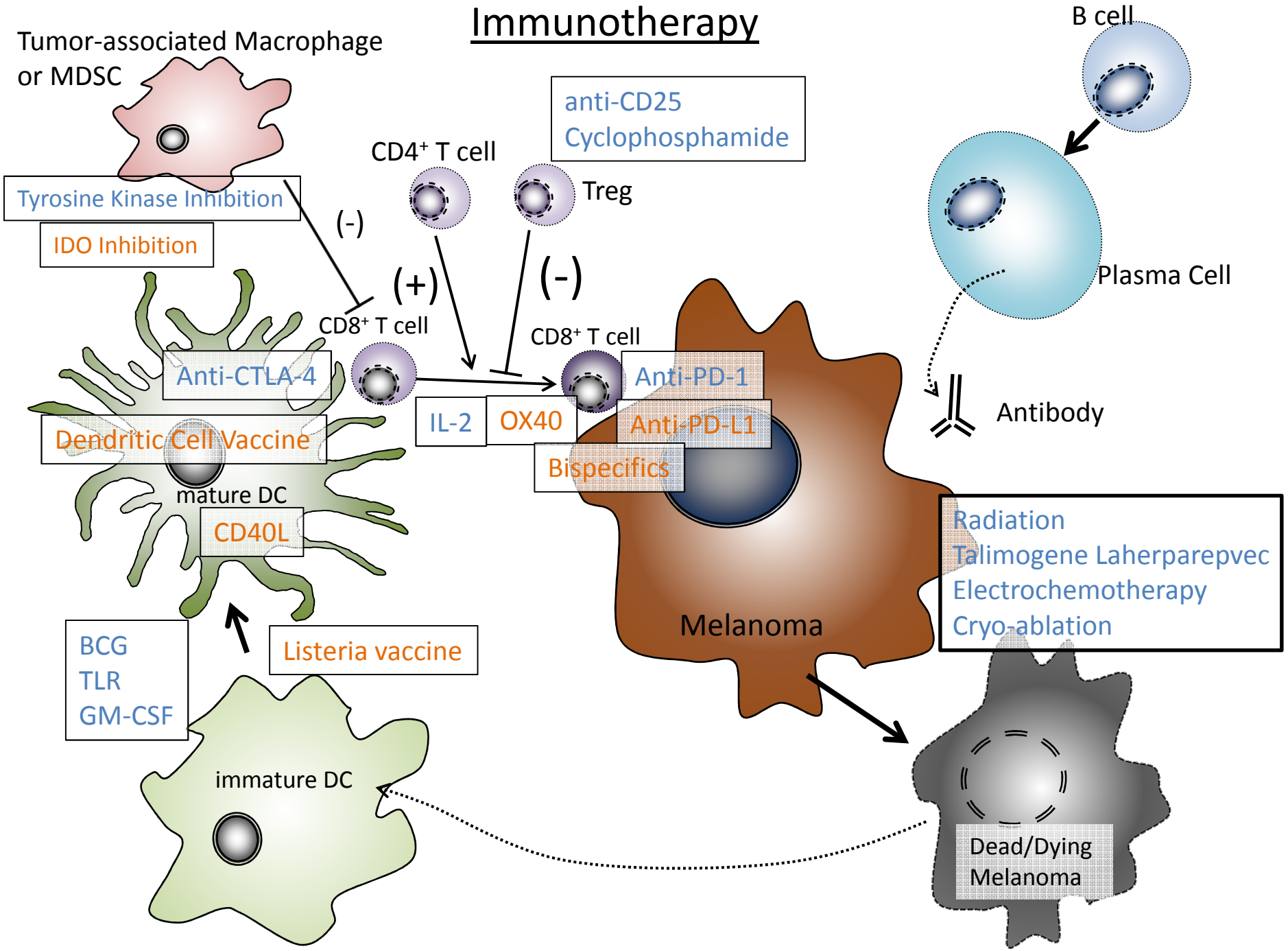
The Immune System and Cancer



Immunomodulation



Is control of the Immune System like driving a car?


Immunotherapy
Tumor-associated Macrophage or MDSC
Tyrosine Kinase Inhibition
IDO Inhibition
(-)
CD4+ T cell
Treg
anti-CD25
Cyclophosphamide
(+)
(-)
CD8+ T cell
CD8+ T cell
Anti-CTLA-4
Dendritic Cell Vaccine
mature DC
CD40L
IL-2
OX40
Anti-PD-1
Anti-PD-L1
Bispecifics
B cell
Plasma Cell
Antibody
Radiation
Talimogene Laherparepvec
Electrochemotherapy
Cryo-ablation
Melanoma
BCG
TLR
GM-CSF
Listeria vaccine
immature DC
Dead/Dying Melanoma

Is control of the Immune System like driving a car?

No…

…more like a space shuttle…

T-Cells

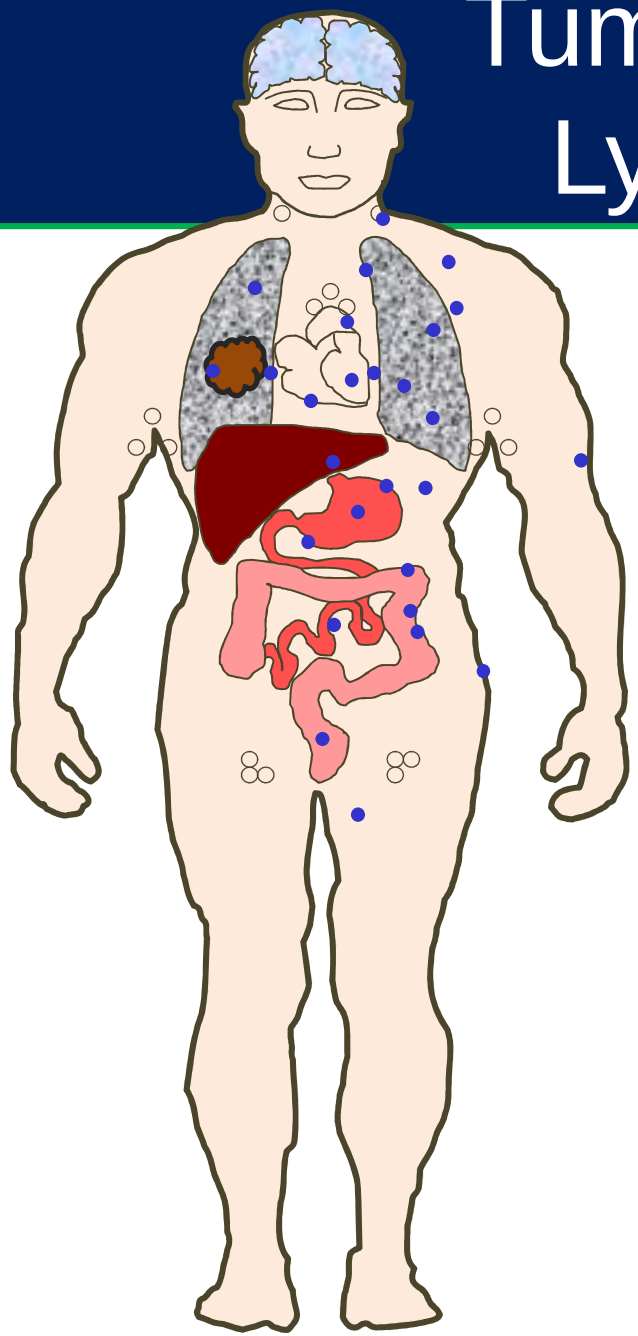
Tumor-Infiltrating Lymphocytes

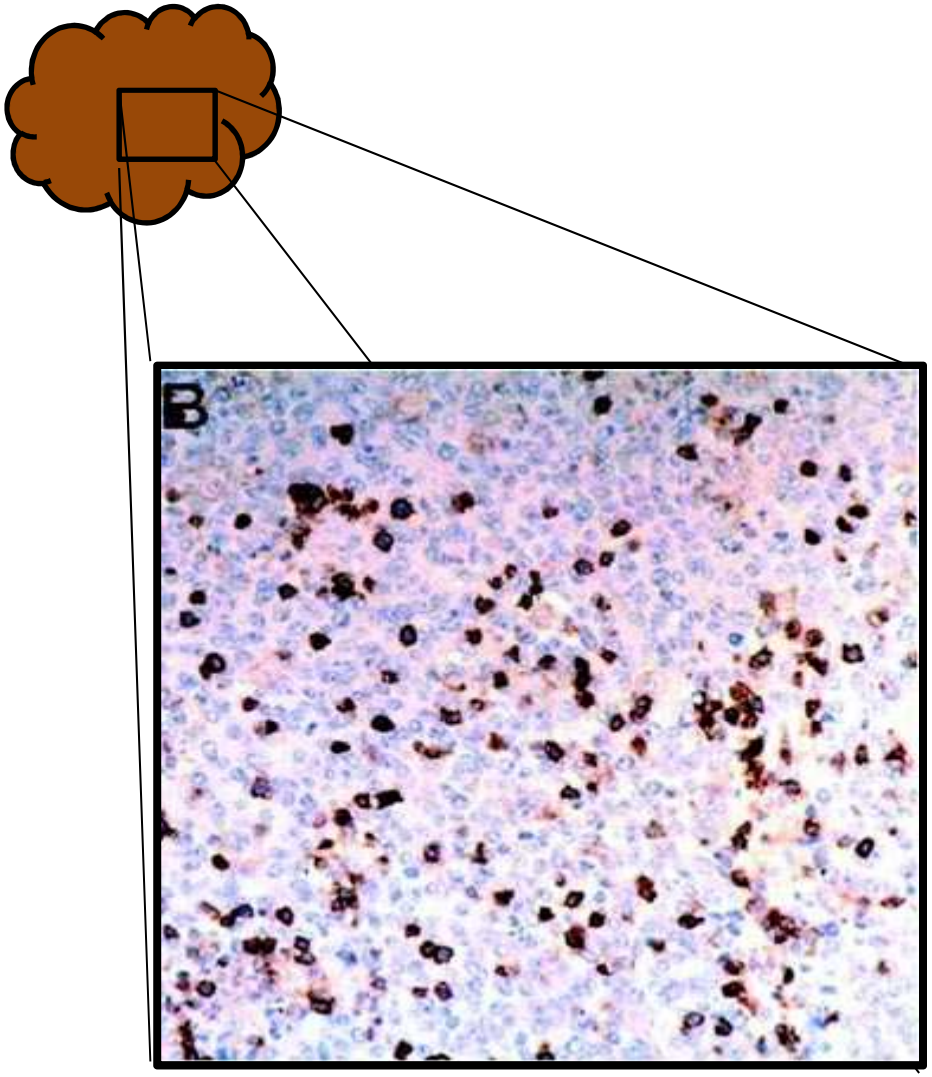
- **Adoptive T-Cell Therapy**

  1) The working model

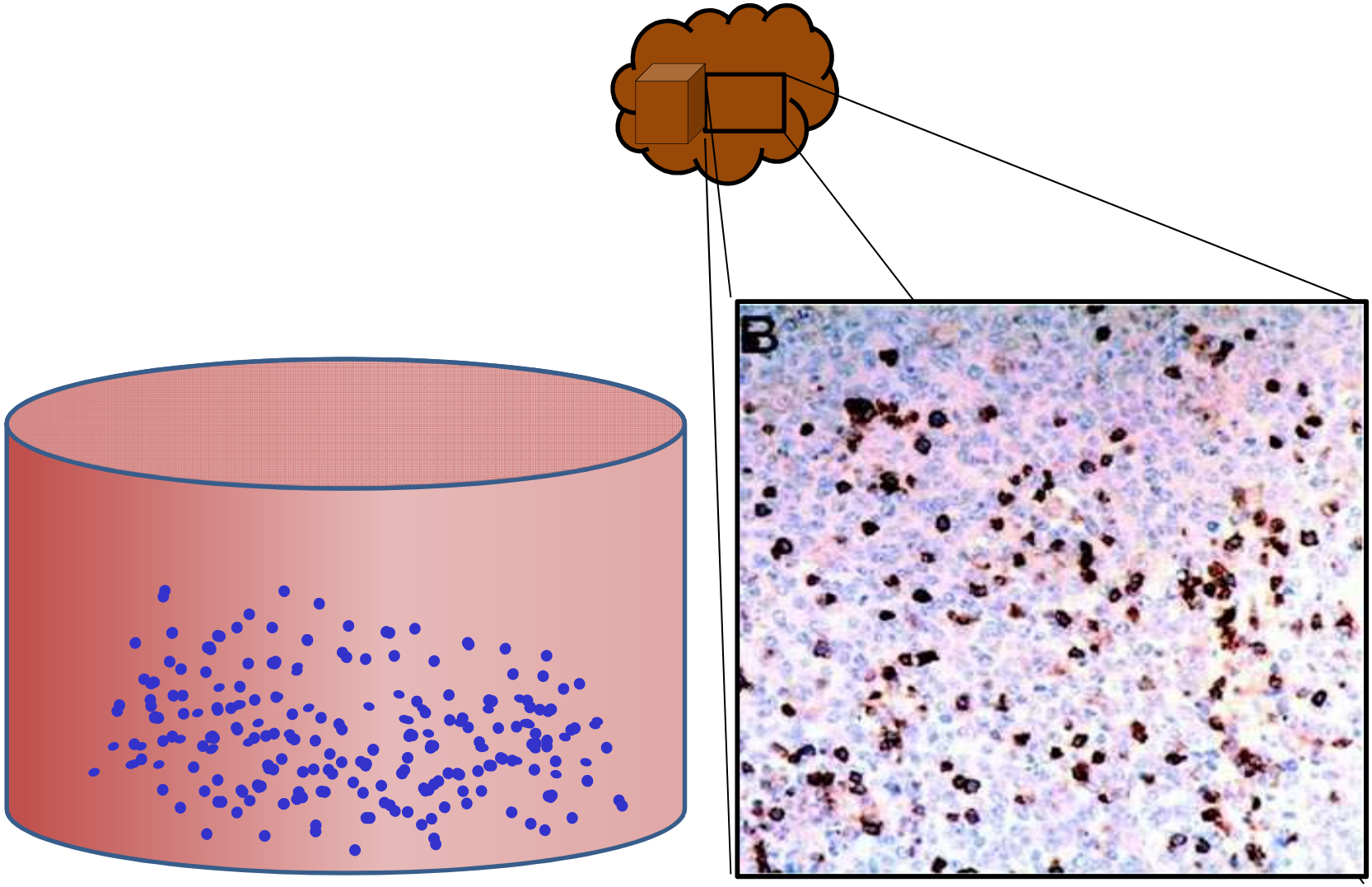
  2) Modifications

Tumor-infiltrating Lymphocytes

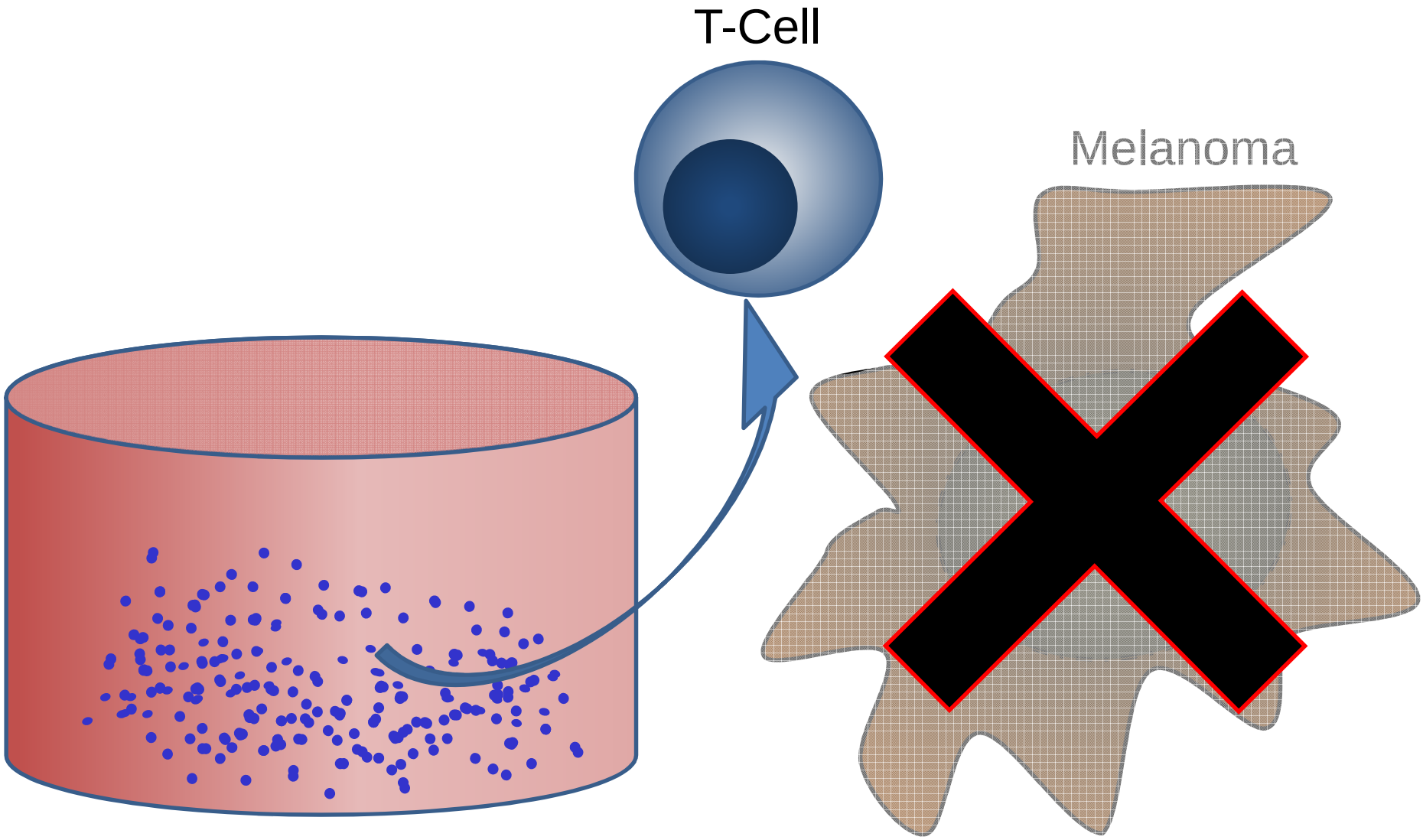




Tumor-infiltrating Lymphocytes



Tumor-infiltrating Lymphocytes

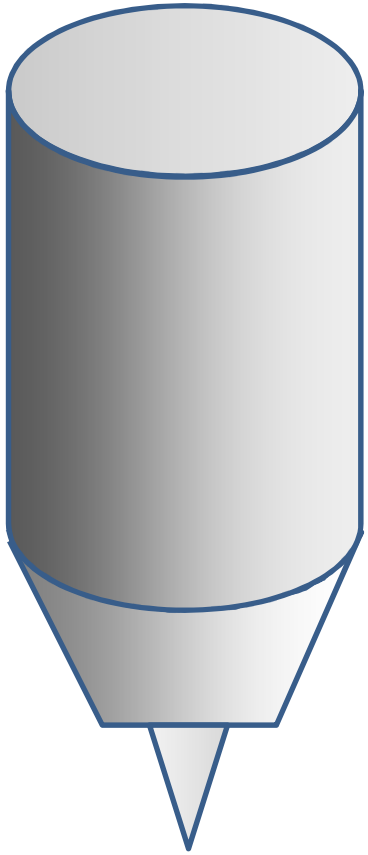


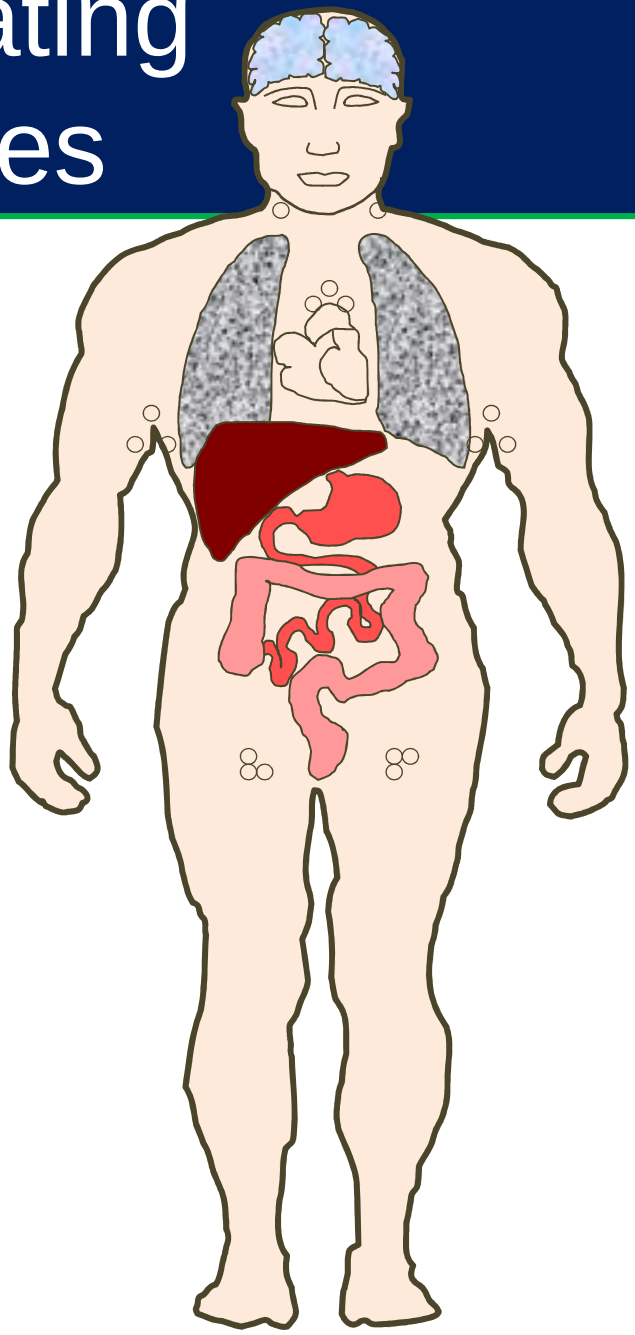
TIL: Current Standard Procedure

T-Cell

RAPID EXPANSION PROTOCOL

Tumor-infiltrating Lymphocytes





TIL: Early Clinical Data

Treatment of Patients With Metastatic Melanoma With Autologous Tumor-Infiltrating Lymphocytes and Interleukin 2

Journal of the National Cancer Institute,
, Vol. 86, No. 15, August 3, 1994

*Steven A. Rosenberg, John R. Yannelli, James C. Yang, Suzanne L. Topalian, Douglas J. Schwartzentruber, Jeffrey S. Weber, David R. Parkinson, Claudia A. Seipp, Jan H. Einhorn, Donald E. White**

Table 2. Number of patients responding to treatment with TILs plus IL-2 and duration of response*

	Response to treatment											
	No cyclophosphamide				Plus cyclophosphamide				Total			
	No. of patients				No. of patients				No. of patients			
	Total	CR	PR	% CR + PR	Total	CR	PR	% CR + PR	Total	CR	PR	% CR + PR
Prior IL-2	11	1	2	27	17	0	6	35	28	1	8	32
No prior IL-2	18	3	3	33	40	1	13	35	58	4	16	34
Total	29	4	5	31	57	1	19	35	86	5	24	34

	Duration of response, mo			
	No cyclophosphamide		Plus cyclophosphamide	
	CR	PR	CR	PR
Prior IL-2	23	4, 1	—	8, 7, 6, 5, 5, 1
No prior IL-2	46+, 38, 21+	7, 4, 2	20	53+, 9, 7, 7, 4, 4

*CR = complete response. PR = partial response.

TIL: Early Clinical Data

Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes

Mark E. Dudley,[1] John R. Wunderlich,[1] Paul F. Robbins,[1] James C. Yang,[1] Patrick Hwu,[1] Douglas J. Schwartzentruber,[1] Suzanne L. Topalian,[1] Richard Sherry,[1] Nicholas P. Restifo,[1] Amy M. Hubicki,[1] Michael R. Robinson,[2] Mark Raffeld,[3] Paul Duray,[3] Claudia A. Seipp,[1] Linda Rogers-Freezer,[1] Kathleen E. Morton,[1] Sharon A. Mavroukakis,[1] Donald E. White,[1] Steven A. Rosenberg[1]*

25 OCTOBER 2002 VOL 298 SCIENCE

Table 1. Patient demographics, treatments received, and clinical outcomes.

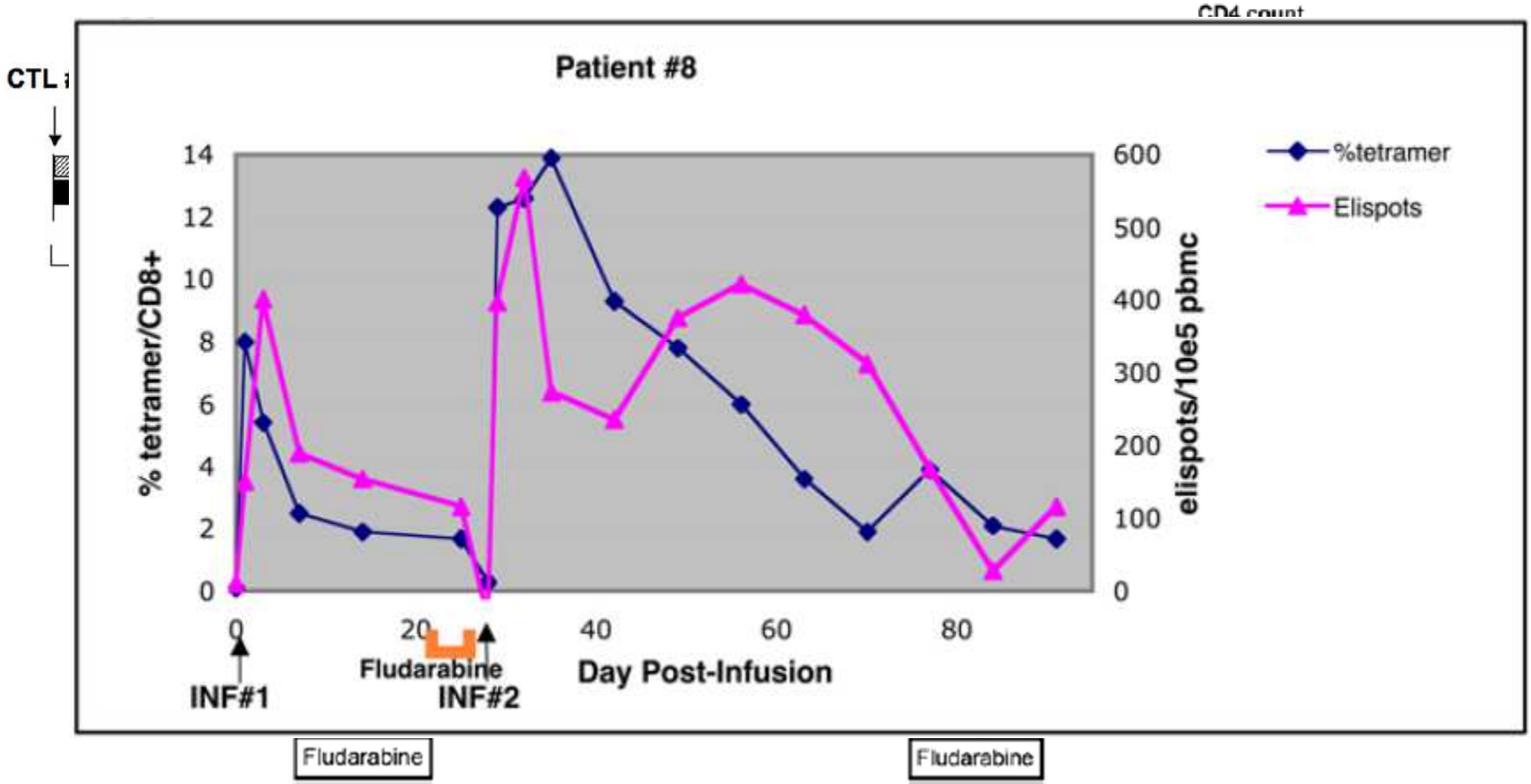
Patient	Age/sex	Treatment*				Sites of evaluable metastases	Response duration‖ (months)	Autoimmunity
		Cells infused† ($\times 10^{-10}$)	CD8/CD4 phenotype‡ (%)	Antigen specificity§	IL-2 (doses)			
1	18/M	2.3	11/39	Other	9	Lymph nodes (axillary, mesenteric, pelvic)	PR¶ (24+)	None
2	30/F	3.5	83/15	MART-1, gp100	8	Cutaneous, subcutaneous	PR (8)	Vitiligo
3	43/F	4.0	44/58	gp100	5	Brain, cutaneous, liver, lung	NR	None
4	57/F	3.4	56/52	gp100	9	Cutaneous, subcutaneous	PR (2)	None
5	53/M	3.0	16/85	Other	7	Brain, lung, lymph nodes	NR-mixed	None
6	37/F	9.2	65/35	Other	6	Lung, intraperitoneal, subcutaneous	PR (15+)	None
7	44/M	12.3	61/41	MART-1	7	Lymph nodes, subcutaneous	NR-mixed	Vitiligo
8	48/M	9.5	48/52	gp100	12	Subcutaneous	NR	None
9	57/M	9.6	84/13	MART-1	10	Cutaneous, subcutaneous	PR (10+)	Vitiligo
10	55/M	10.7	96/2	MART-1	12	Lymph nodes, cutaneous, subcutaneous	PR¶ (9+)	Uveitis
11	29/M	13.0	96/3	MART-1	12	Liver, pericardial, subcutaneous	NR-mixed	Vitiligo
12	37/F	13.7	72/24	MART-1	11	Liver, lung, gallbladder, lymph nodes	NR-mixed	None
13	41/F	7.7	92/8	MART-1	11	Subcutaneous	NR	None

Lymphodepletion

Fludarabine Modulates Immune Response and Extends *In Vivo* Survival of Adoptively Transferred CD8 T Cells in Patients with Metastatic Melanoma

Herschel Wallen*, John A. Thompson, J. Zachary Reilly, Rebecca M. Rodmyre, Jianhong Cao, Cassian Yee

March 2009 | Volume 4 | Issue 3 | e4749

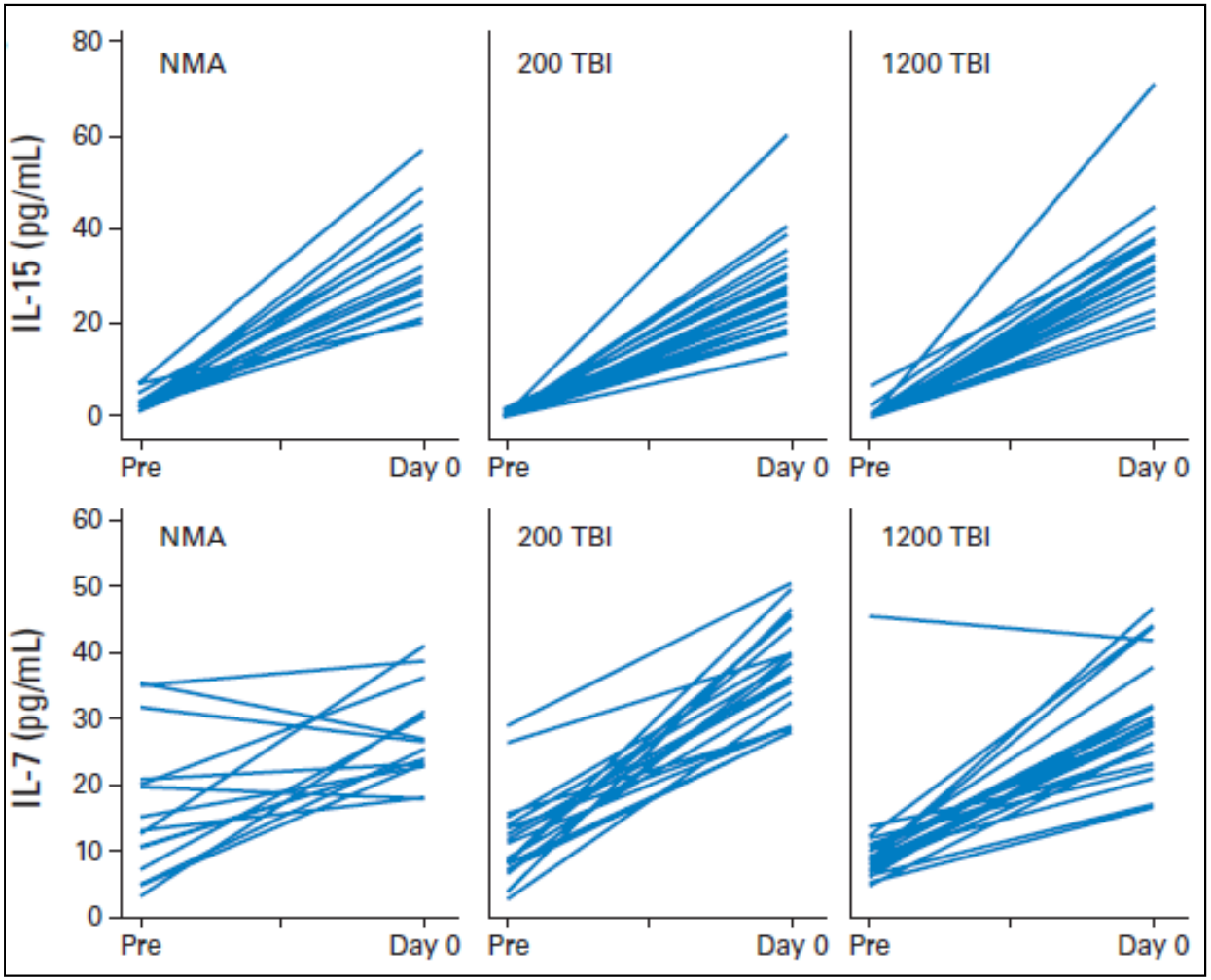


Lymphodepletion

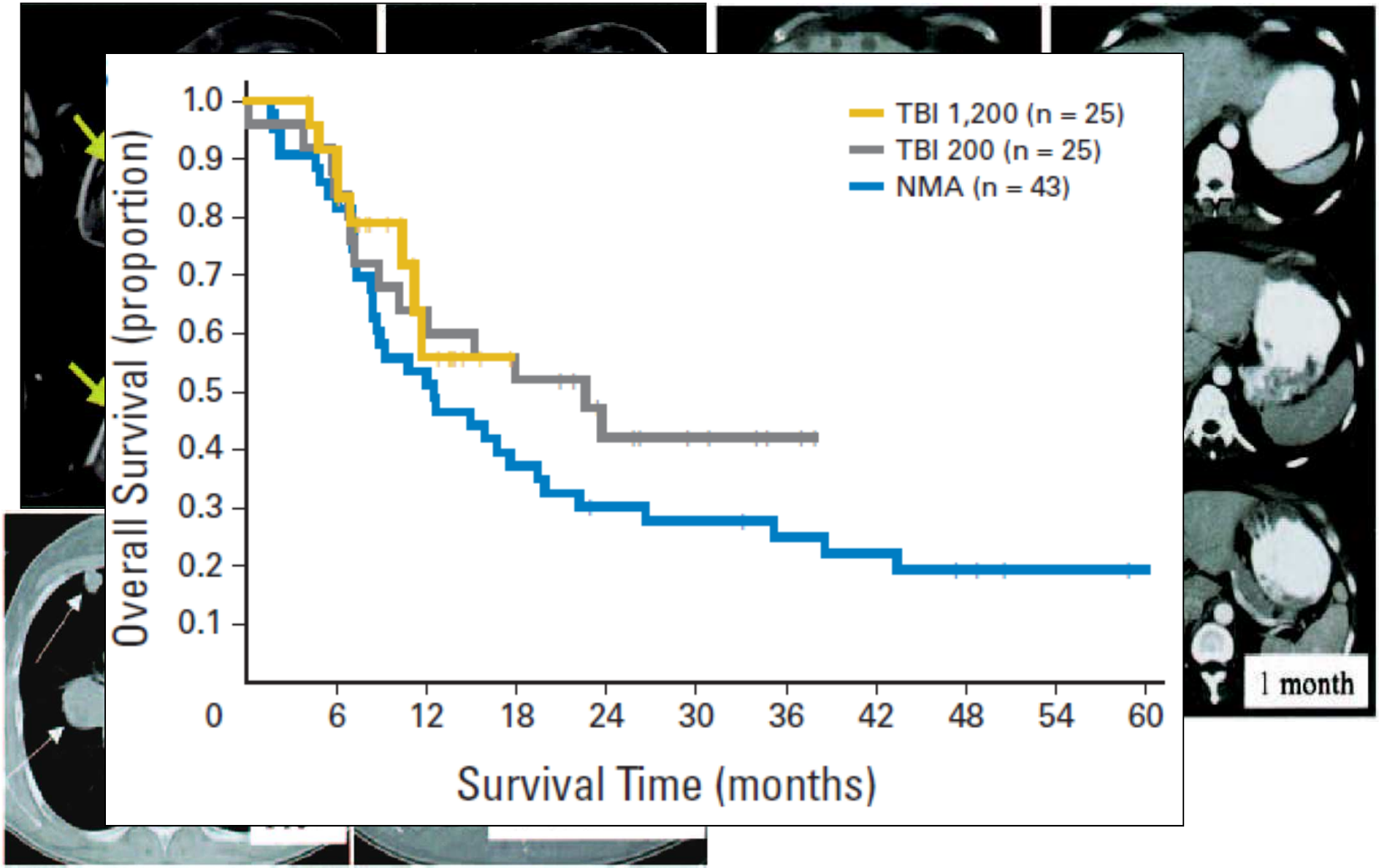
Adoptive Cell Therapy for Patients With Metastatic Melanoma: Evaluation of Intensive Myeloablative Chemoradiation Preparative Regimens

Mark E. Dudley, James C. Yang, Richard Sherry, Marybeth S. Hughes, Richard Royal, Udai Kammula, Paul F. Robbins, JianPing Huang, Deborah E. Citrin, Susan F. Leitman, John Wunderlich, Nicholas P. Restifo, Armen Thomasian, Stephanie G. Downey, Franz O. Smith, Jacob Klapper, Kathleen Morton, Carolyn Laurencot, Donald E. White, and Steven A. Rosenberg

JOURNAL OF CLINICAL ONCOLOGY
VOLUME 26 · NUMBER 32 · NOVEMBER 10 2008



TIL: Clinical Responses

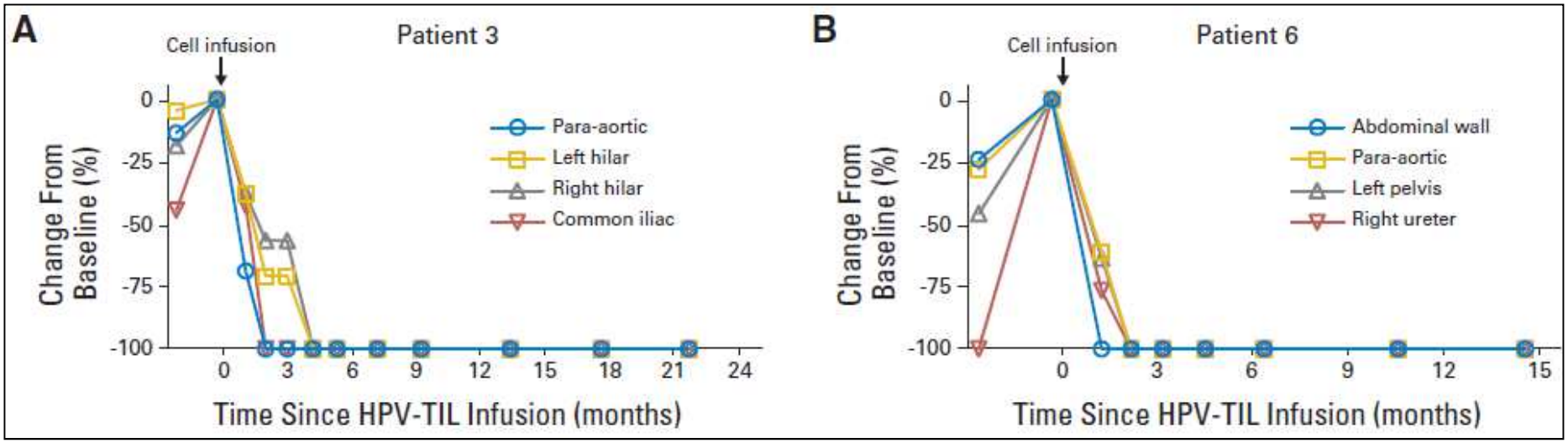


Other Tumors

Complete Regression of Metastatic Cervical Cancer After Treatment With Human Papillomavirus–Targeted Tumor-Infiltrating T Cells

Sanja Stevanović, Lindsey M. Draper, Michelle M. Langhan, Tracy E. Campbell, Mei Li Kwong, John R. Wunderlich, Mark E. Dudley, James C. Yang, Richard M. Sherry, Udai S. Kammula, Nicholas P. Restifo, Steven A. Rosenberg, and Christian S. Hinrichs

JOURNAL OF CLINICAL ONCOLOGY MAY 10 2015

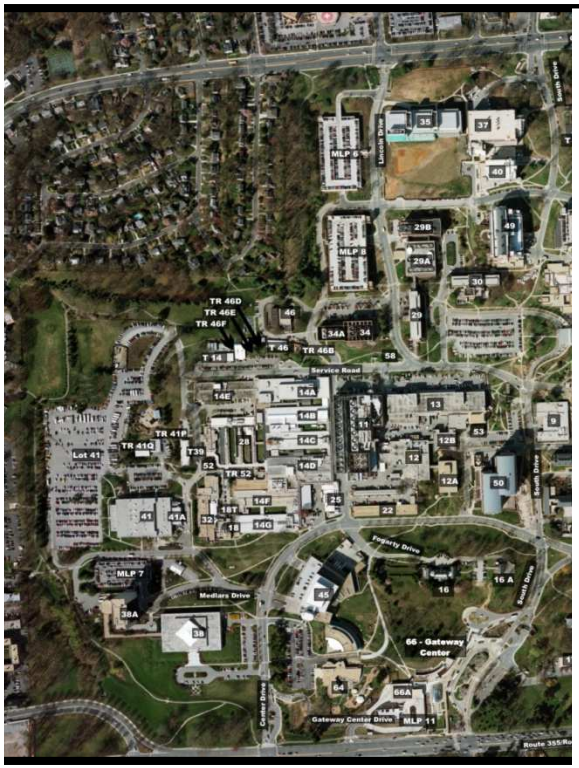


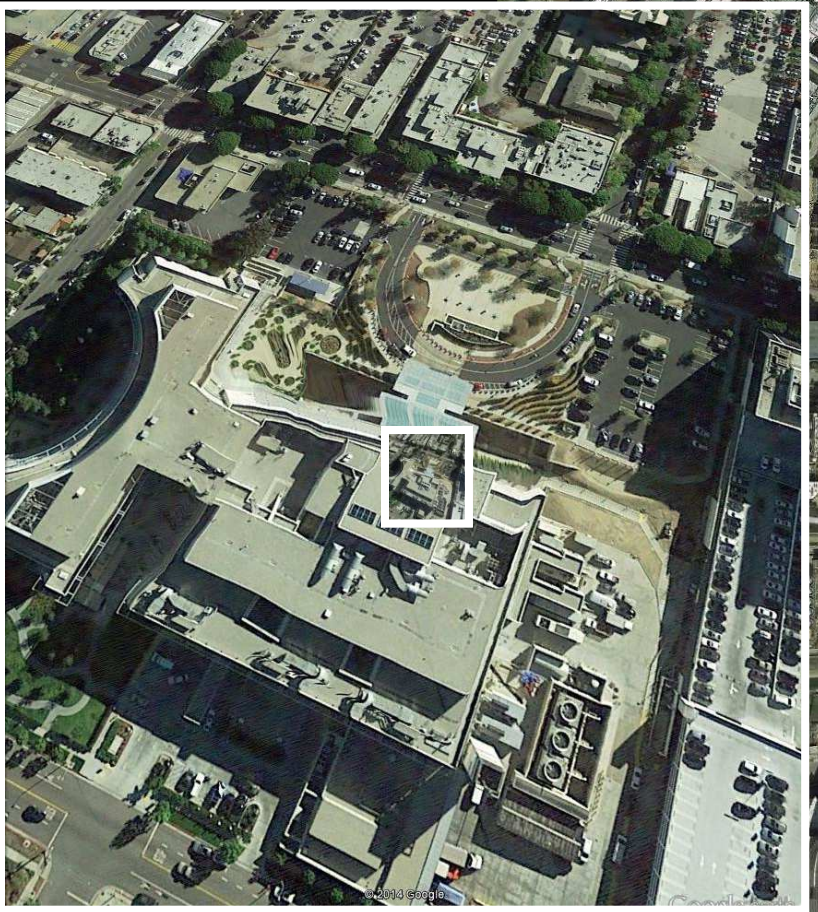
Tumor-Infiltrating Lymphocytes: Challenges

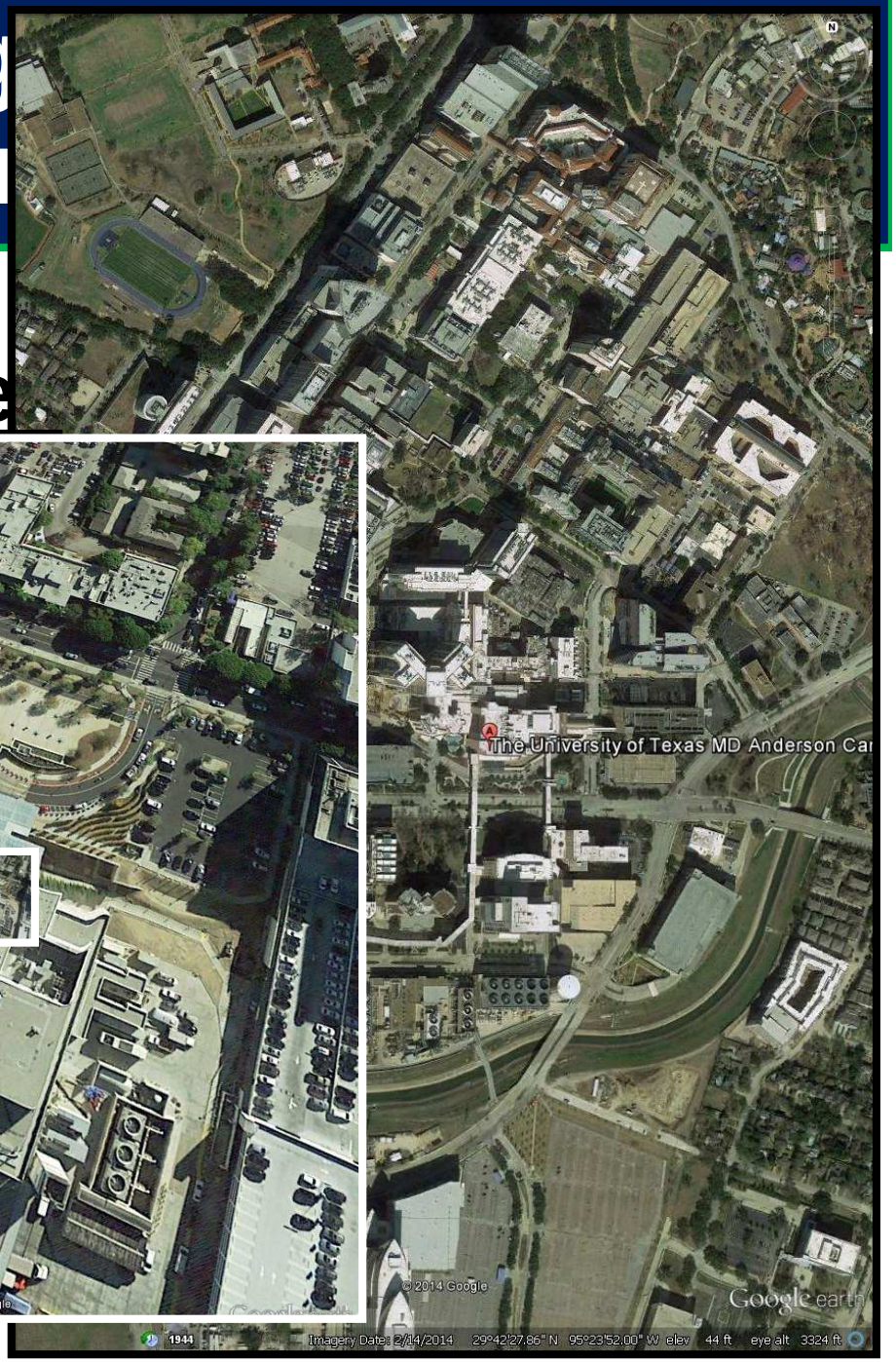
- **Technical challenges: (“GMP”)**
- **Timeline**
- **Tumor reactivity**
- **Interleukin-2**

Tumor-Infiltrating
Challe

- **Technical challenge**

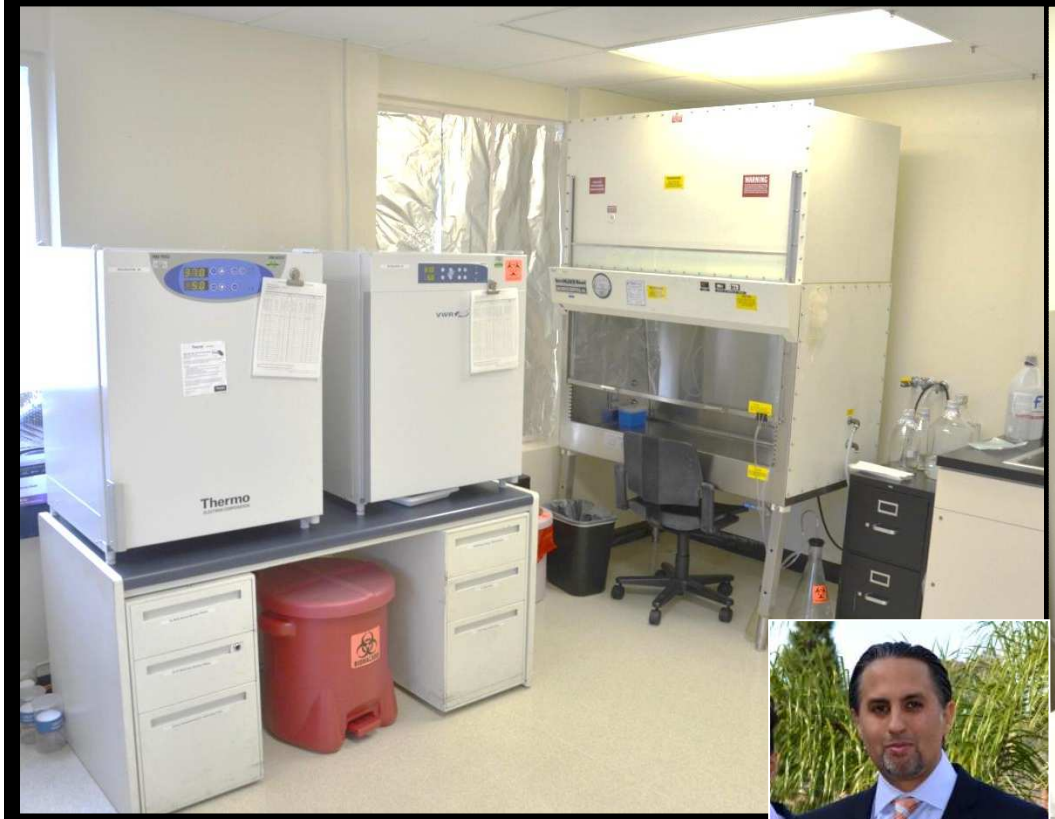






Cell Production Facility

Cell Production Facility



- IND Approved
- Protocol Open/Accruing

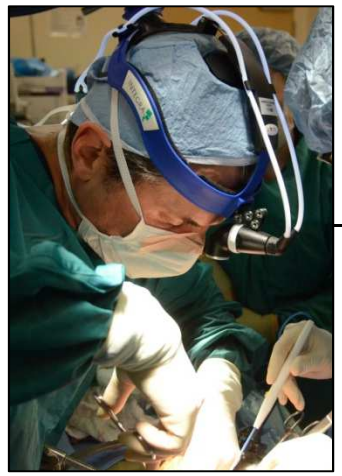
Tumor-Infiltrating Lymphocytes: Challenges

- Technical challenges: (“GMP”)
- **Timeline**
- Tumor reactivity
- Interleukin-2

Tumor-Infiltrating Lymphocytes: Challenges

- Technical challenges: (“GMP”)

- **Timeline**

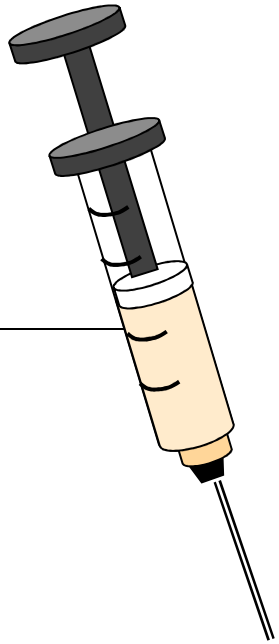


Tumor Removal

2-4 weeks

Testing

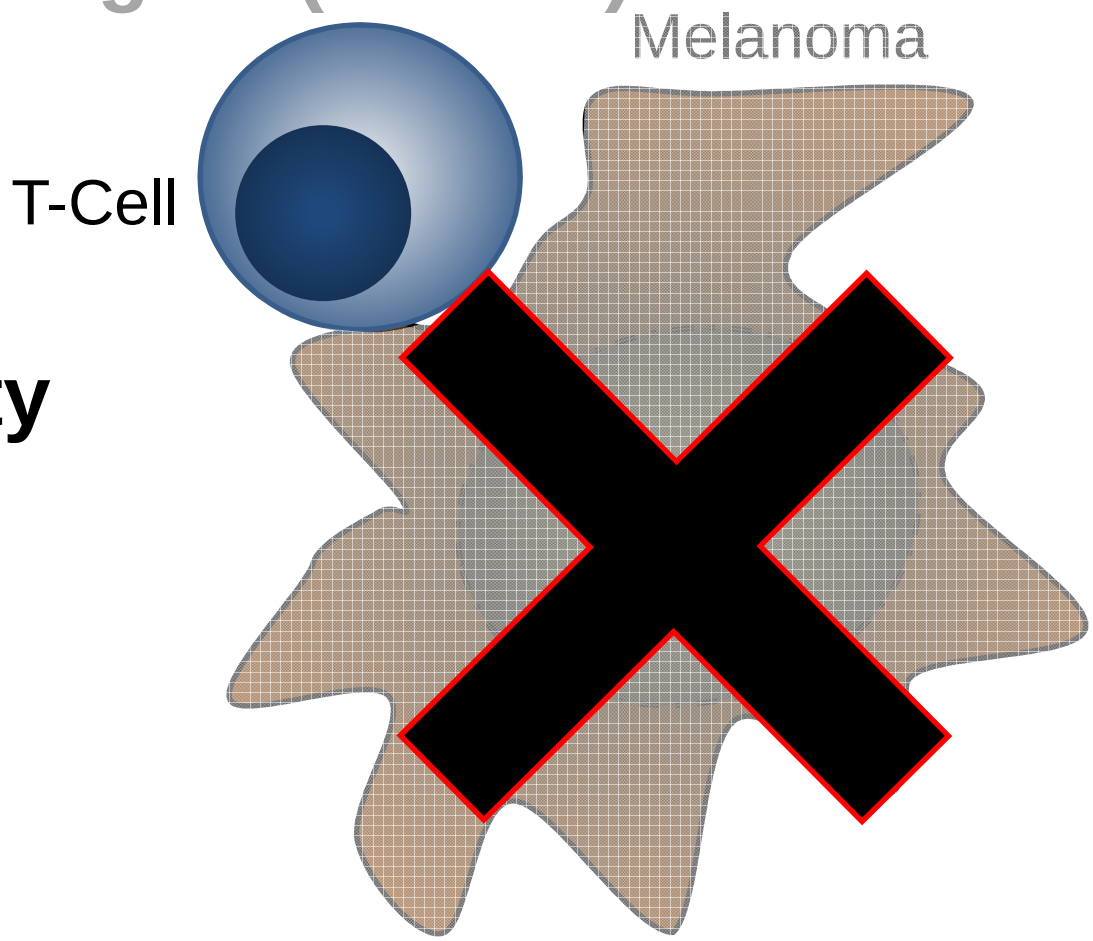
2 weeks



5-8 weeks

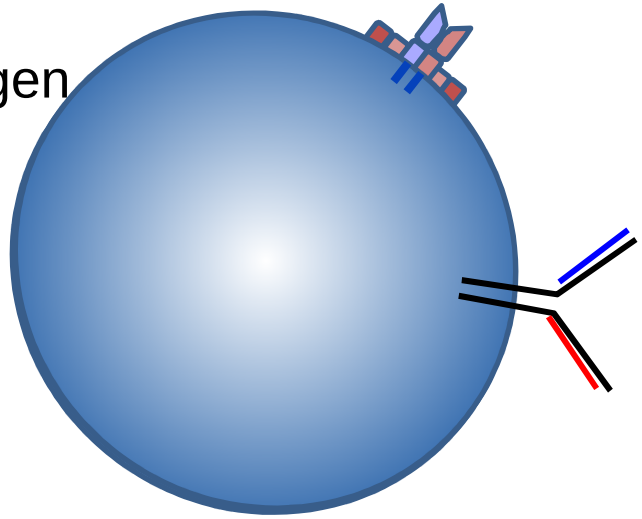
Tumor-Infiltrating Lymphocytes: Challenges

- Technical challenges: (“GMP”)
- Timeline
- **Tumor reactivity**
- Interleukin-2

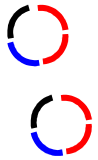


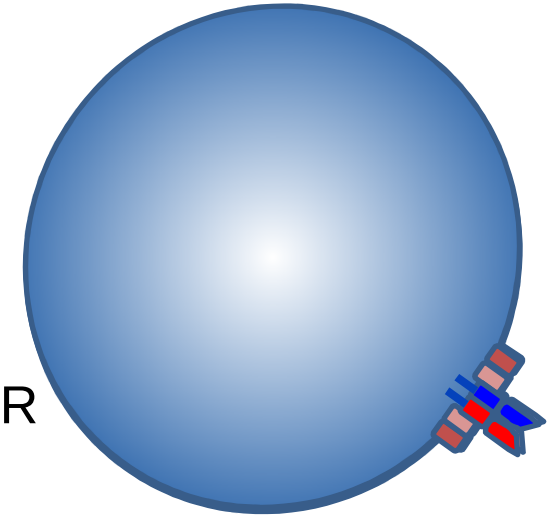
Modified T-cells

Chimeric Antigen Receptor

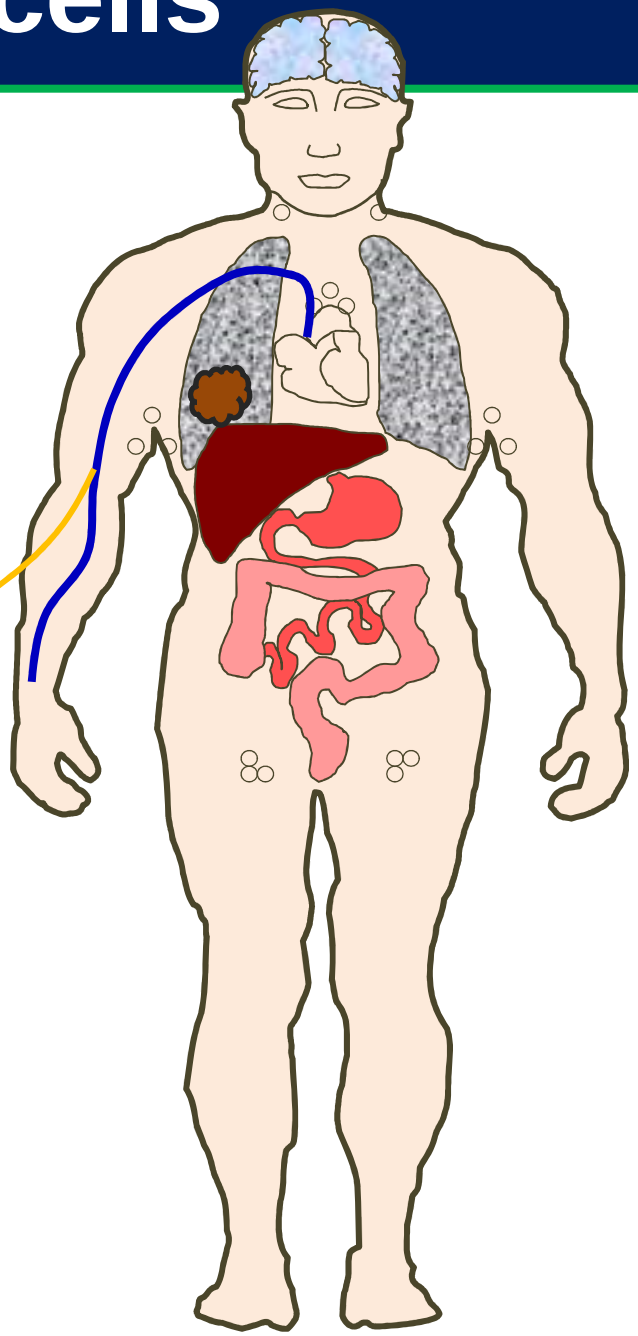


Peripheral Blood

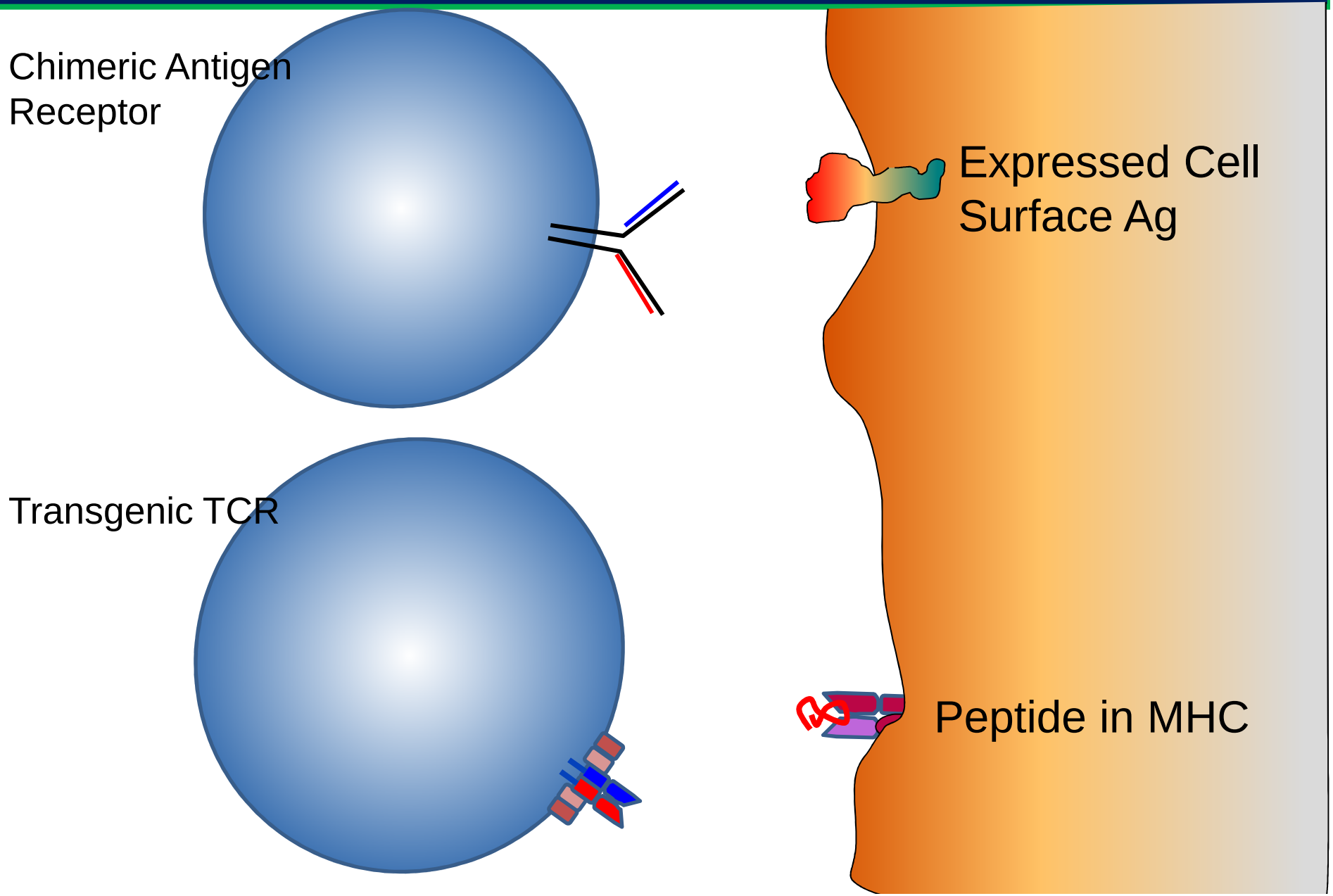




Transgenic TCR



Modified T-cells: Antigens

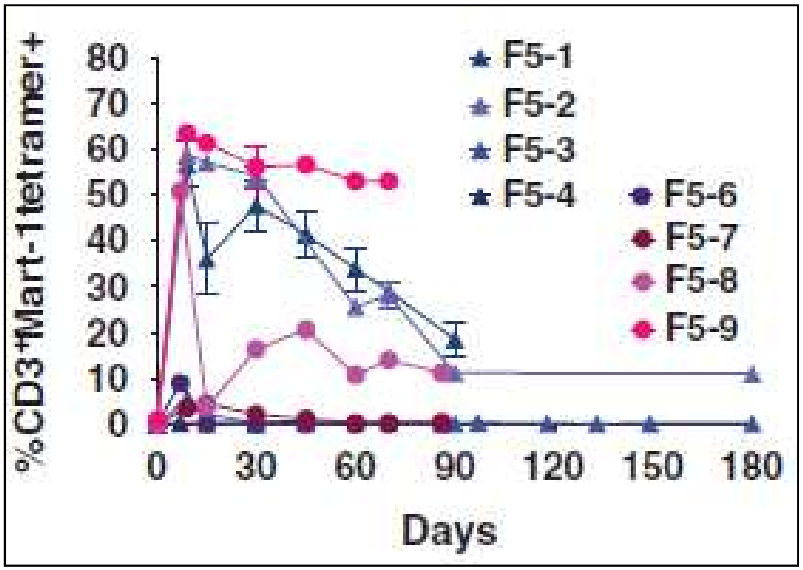


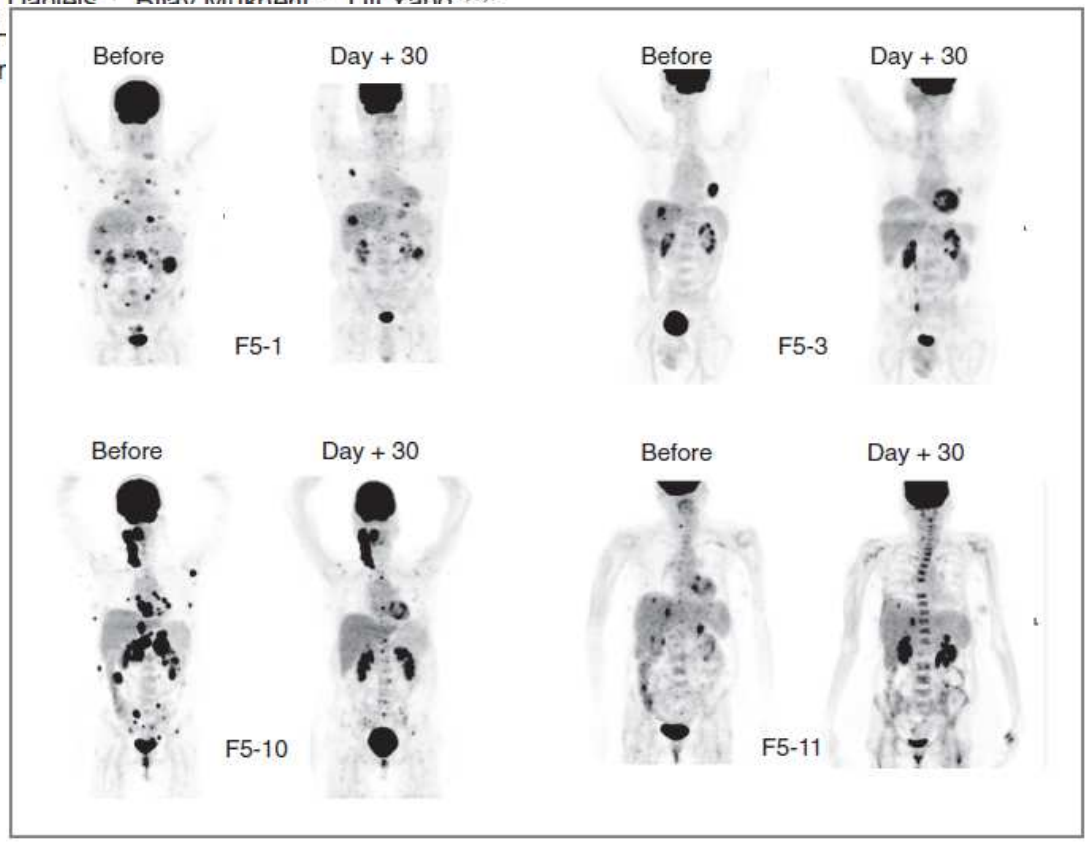
Transgenic TCR

Adoptive Transfer of MART-1 T-Cell Receptor Transgenic Lymphocytes and Dendritic Cell Vaccination in Patients with Metastatic Melanoma

Thinle Chodon[1,18], Begoña Comin-Anduix[2,6], Bartosz Chmielowski[1,6], Richard C. Koya[2,6,18], Zhongqi Wu[1], Martin Auerbach[5], Charles Ng[1], Earl Avramis[1], Elizabeth Seja[1], Arturo Villanueva[1], Tara A. McCannel[7], Akira Ishiyama[2], Johannes Czernin[5,6], Caius G. Radu[5,6], Xiaoyan Wang[1], David W. Gjertson[3], Alistair J. Cochran[3], Kenneth Cornetta[14], Deborah J.L. Wong[1], Paula Kaplan-Lefko[1], Omid Hamid[10], Wolfram Samlowski[15], Peter A. Cohen[16], Gregory A. Daniels[11], Bijay Mukherji[17], Lili Yang[4,6,8], Jerome A. Zack[1,6,8], Donald B. Kohn[4,6,8], James R. H[illegible], David Baltimore[13], James S. Economou[2,4,5,6], and Ar[illegible]

Clin Cancer Res; 20(9) May 1, 2014



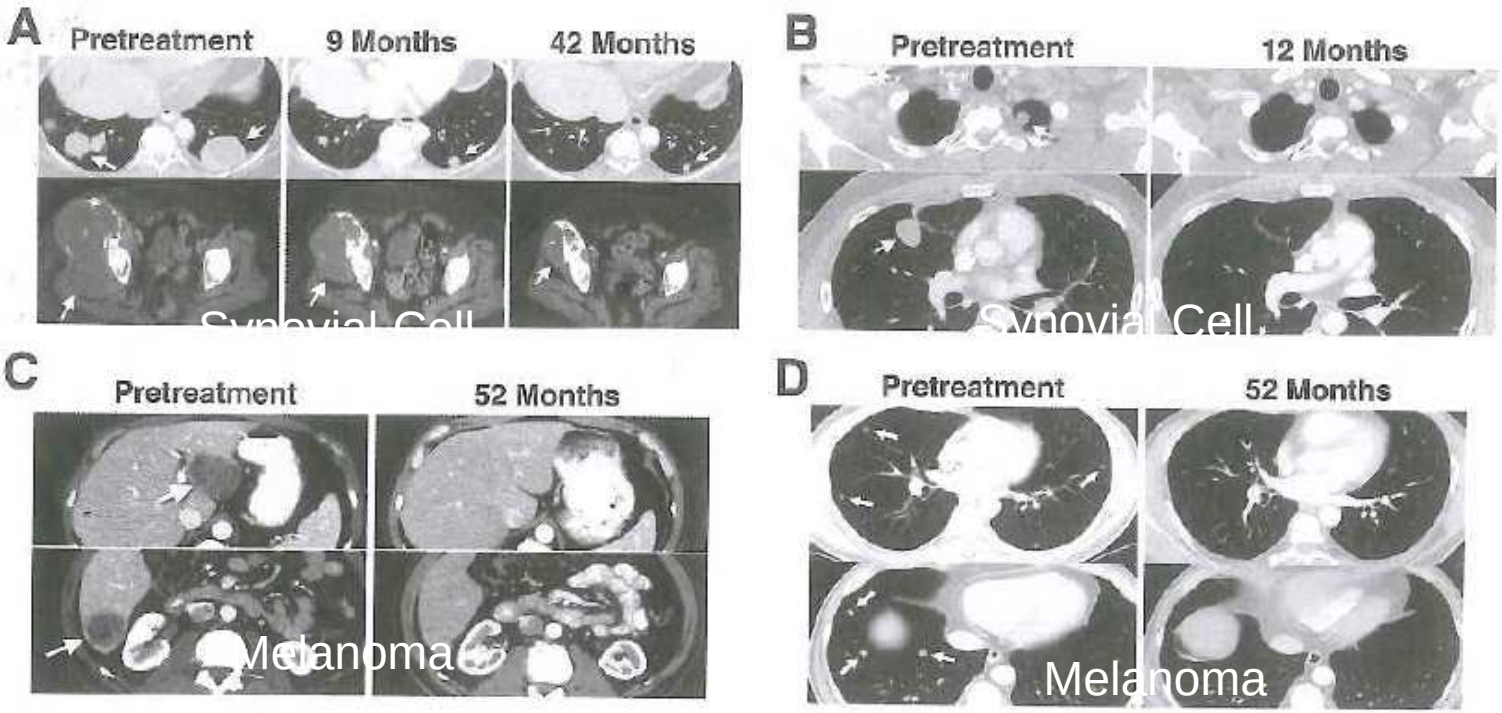


Transgenic TCR

A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1–Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response

Paul F. Robbins[1], Sadik H. Kassim[1], Thai L.N. Tran[2], Jessica S. Crystal[1], Richard A. Morgan[1], Steven A. Feldman[1], James C. Yang[1], Mark E. Dudley[1], John R. Wunderlich[1], Richard M. Sherry[1], Udai S. Kammula[1], Marybeth S. Hughes[1], Nicholas P. Restifo[1], Mark Raffeld[3], Chyi-Chia R. Lee[3], Yong F. Li[1], Mona El-Gamil[1], and Steven A. Rosenberg[1]

Clin Cancer Res; 21(5) March 1, 2015

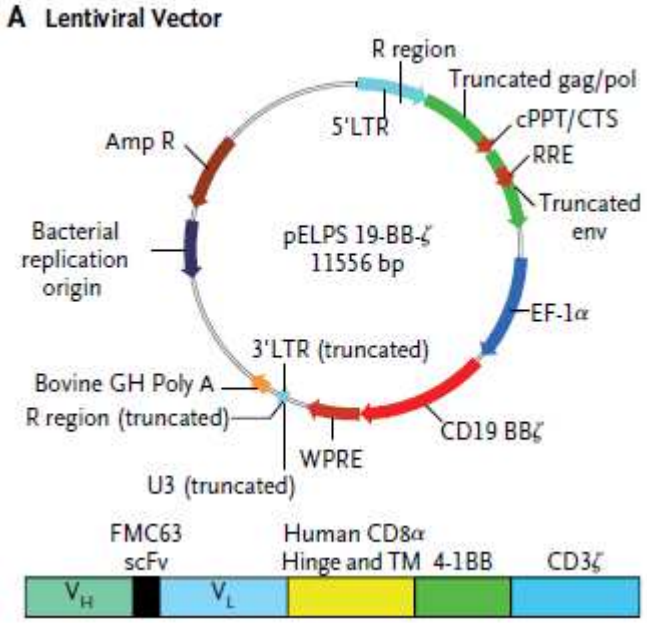


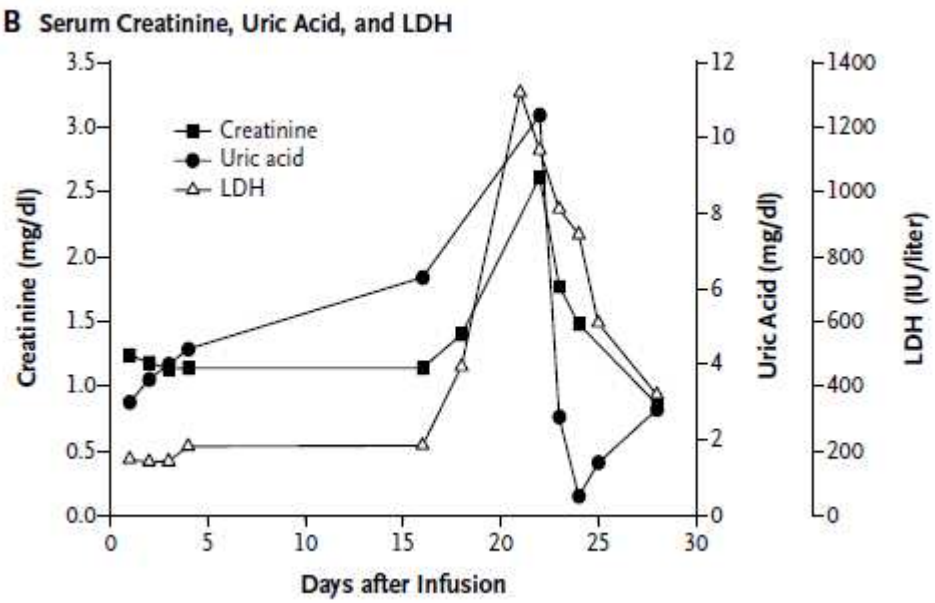
Chimeric Antigen Receptor T-Cells

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

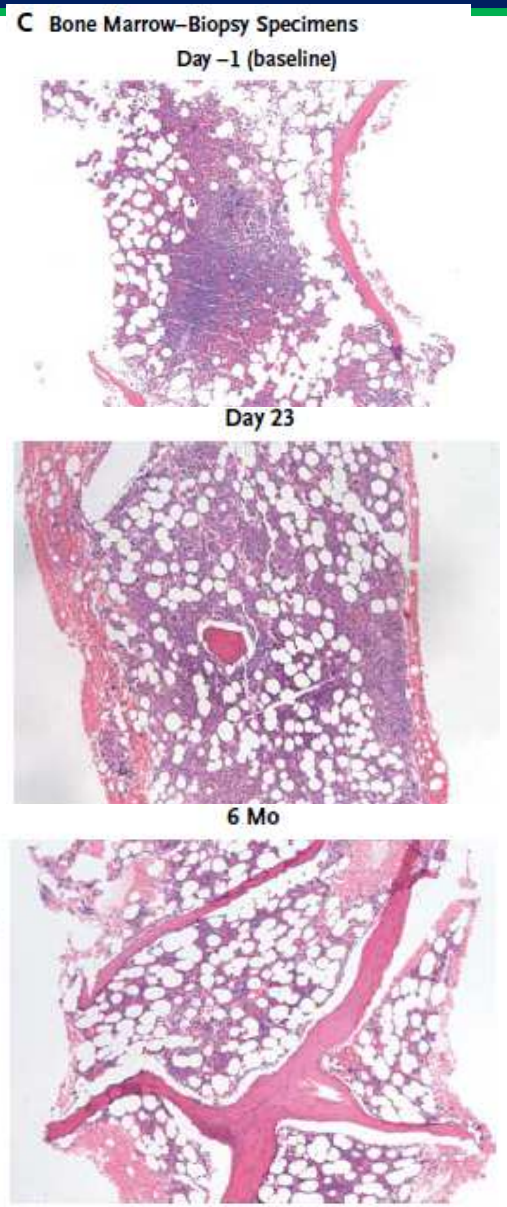
David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

The NEW ENGLAND JOURNAL of MEDICINE
August 10, 2011,



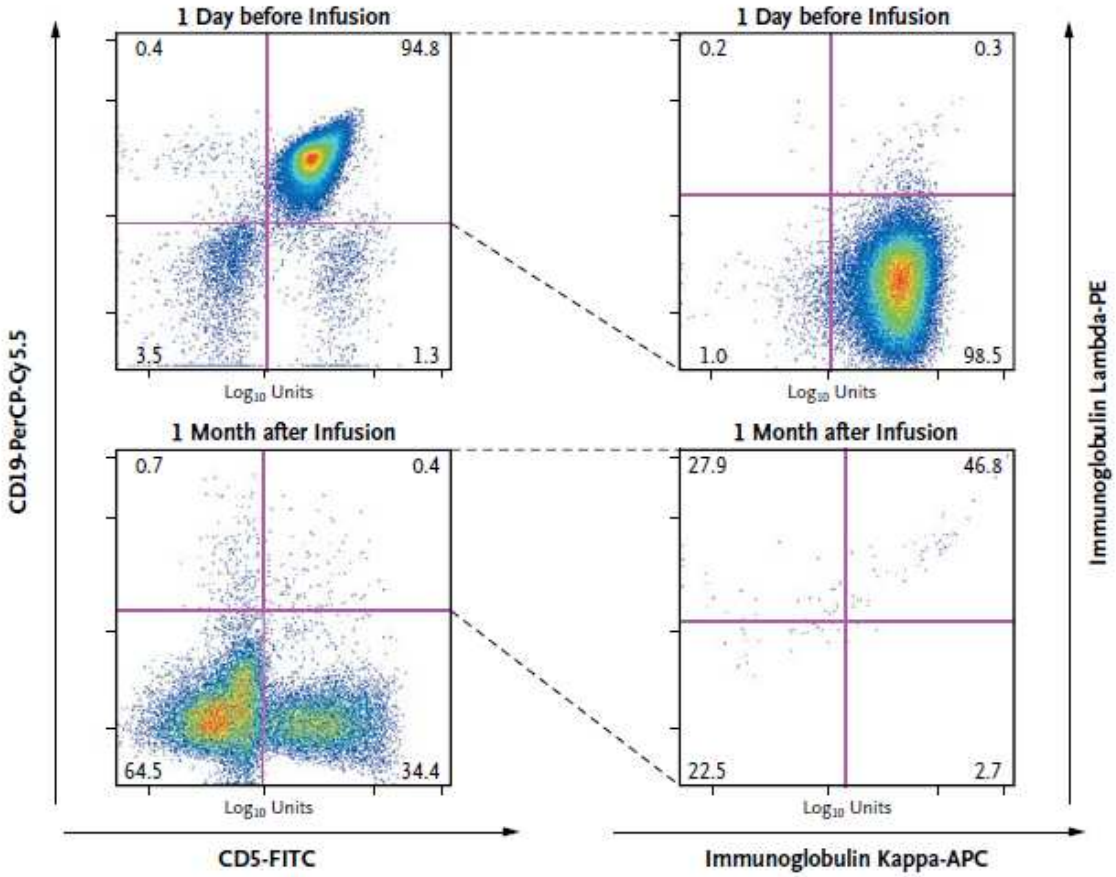


Chimeric Antigen Receptor T-Cells



Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

The NEW ENGLAND JOURNAL of MEDICINE
August 10, 2011,



Chimeric Antigen Receptor T-Cells

Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

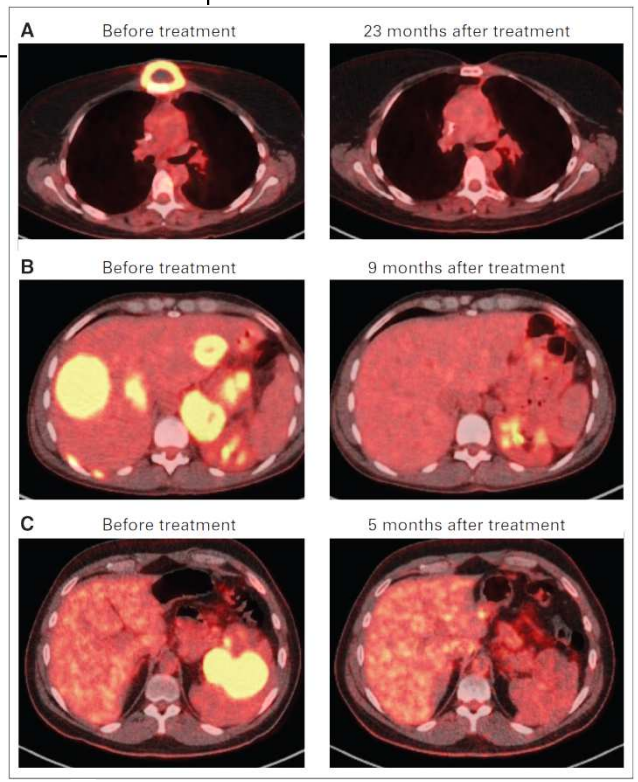
James N. Kochenderfer, Mark E. Dudley, Sadik H. Kassim, Robert P.T. Somerville, Robert O. Carpenter, Maryalice Stetler-Stevenson, James C. Yang, Giao Q. Phan, Marybeth S. Hughes, Richard M. Sherry, Mark Raffeld, Steven Feldman, Lily Lu, Yong F. Li, Lien T. Ngo, Andre Goy, Tatyana Feldman, David E. Spaner, Michael L. Wang, Clara C. Chen, Sarah M. Kranick, Avindra Nath, Debbie-Ann N. Nathan, Kathleen E. Morton, Mary Ann Toomey, and Steven A. Rosenberg

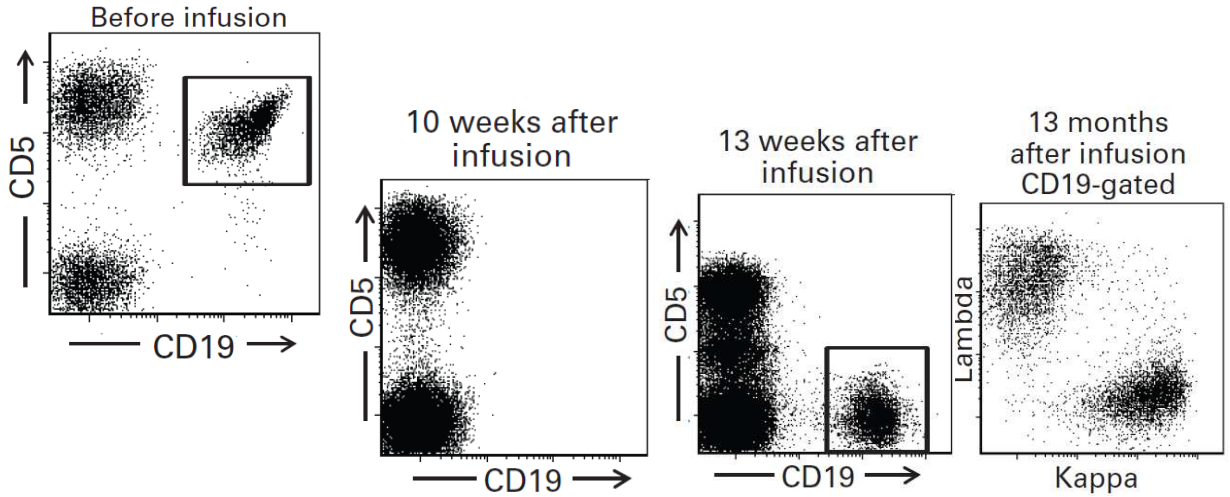
JOURNAL OF CLINICAL ONCOLOGY **Published Ahead of Print on August 25, 2014**

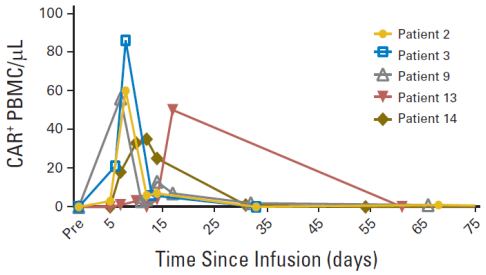
Chimeric Antigen Receptor T-Cells

Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

- 15 patients (9 DLBCL, 6 indolent B-cell malig.)
- 1 Death and several neurologic toxicities
- 4/7 DLBCL with CR, 2 PR, 1 SD
- Overall RR: 12/13 (92%) (9 responses ongoing)







CAR T-Cells: Toxicity

- **Cytokine Release Syndrome**

Case Report of a Serious Adverse Event Following the Administration of T Cells Transduced With a Chimeric Antigen Receptor Recognizing *ERBB2*

Richard A Morgan[1], James C Yang[1], Mio Kitano[1], Mark E Dudley[1], Carolyn M Laurencot[1] and Steven A Rosenberg[1]

Molecular Therapy vol. 18 no. 4, 843–851 apr. 2010

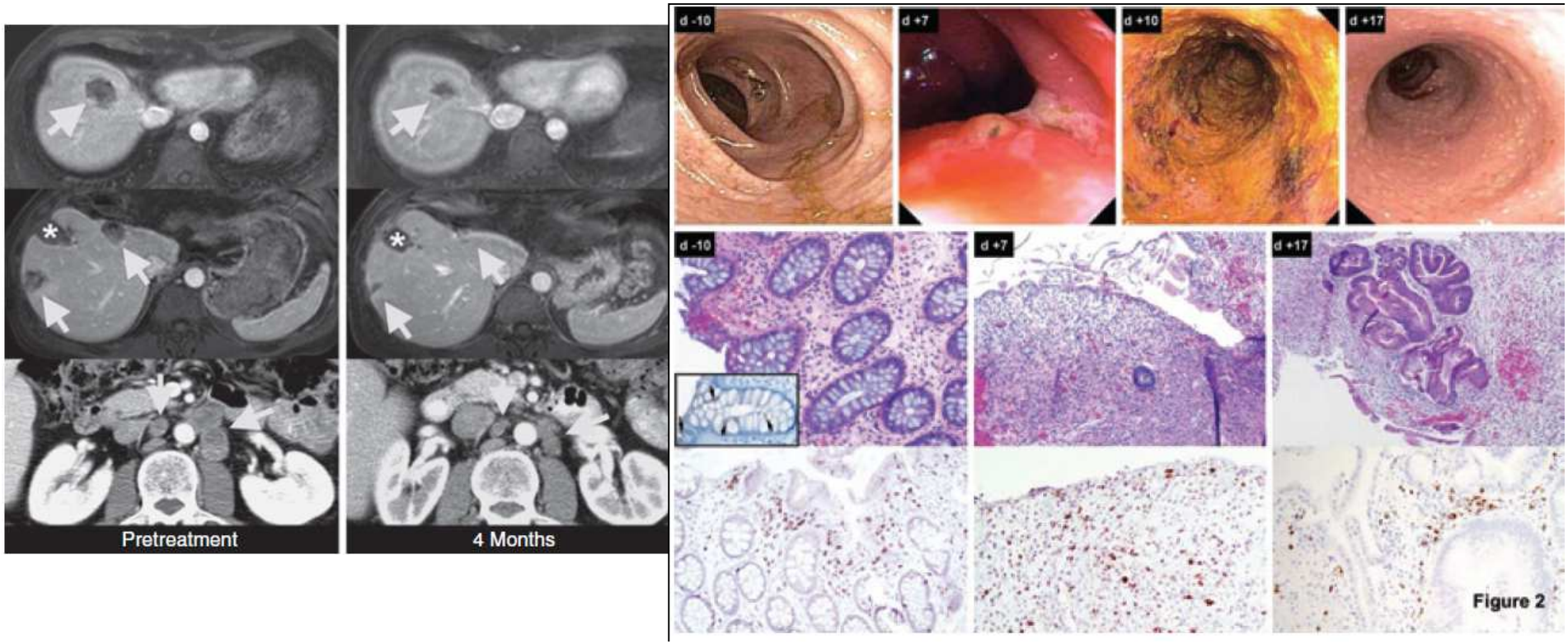
- 39 year-old with metastatic colorectal cancer
- 100 billion ERBB2 CAR T cells
- 15 minutes after infusion, respiratory distress, hypotension
- Died 5 days later

CAR T-Cells:"On Target – Off Tumor"

T Cells Targeting Carcinoembryonic Antigen Can Mediate Regression of Metastatic Colorectal Cancer but Induce Severe Transient Colitis

Maria R Parkhurst[1], James C Yang[1], Russell C Langan[1], Mark E Dudley[1], Debbie-Ann N Nathan[1], Steven A Feldman[1], Jeremy L Davis[1], Richard A Morgan[1], Maria J Merino[2], Richard M Sherry[1], Marybeth S Hughes[1], Udai S Kammula[1], Giao Q Phan[1], Ramona M Lim[3], Stephen A Wank[3], Nicholas P Restifo[1], Paul F Robbins[1], Carolyn M Laurencot[1] and Steven A Rosenberg[1]

Molecular Therapy vol. 19 no. 3 mar. 2011



Toxicity

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

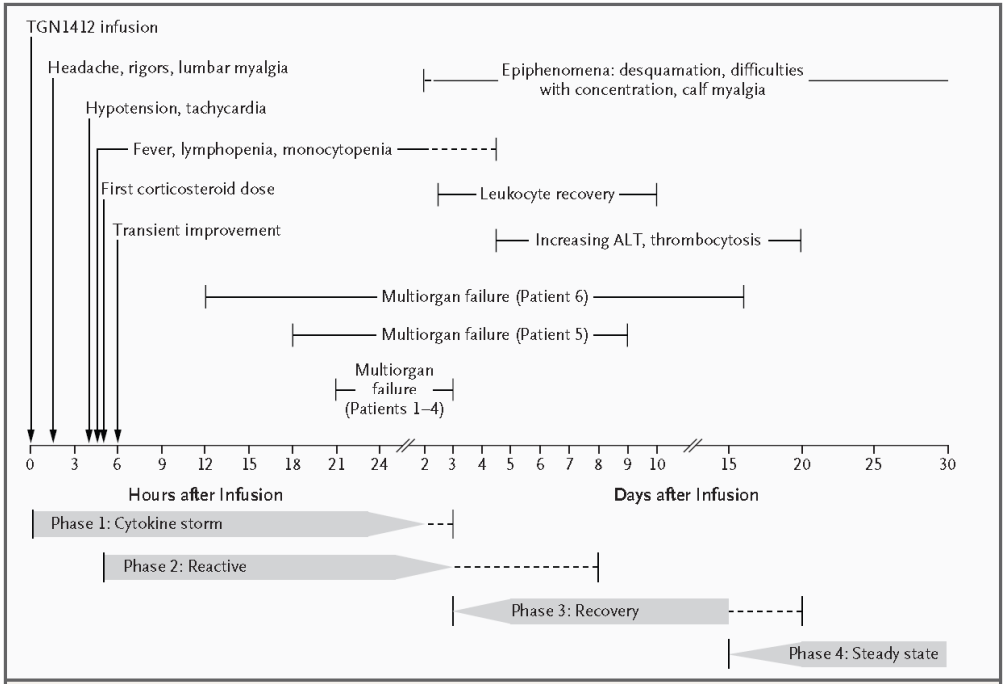
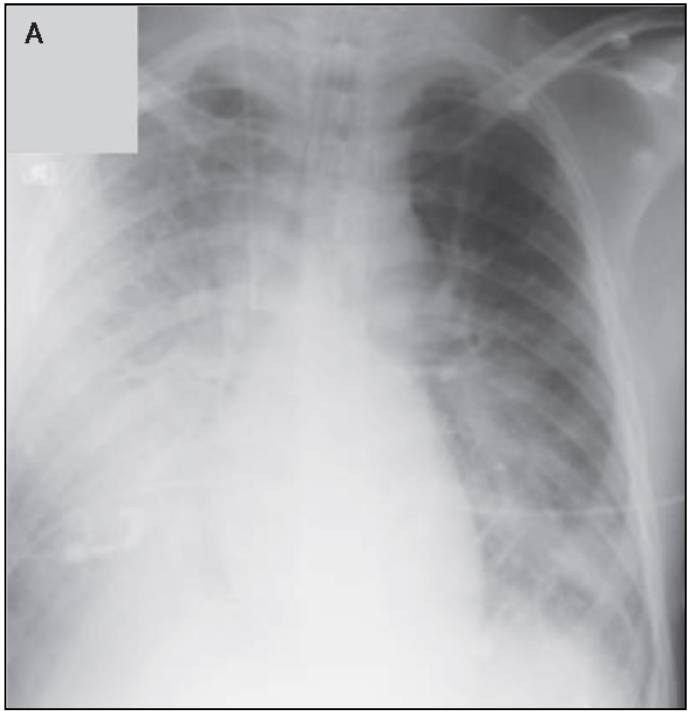


Figure 1. Summary Timeline of the Main Events after Infusion of TGN1412.

The course is divided into four phases: cytokine storm, reactive, recovery, and steady state. ALT denotes alanine aminotransferase. Dashed lines represent the responses of Patients 5 and 6 (who were the most seriously ill).



Toxicity

Clinical Experiences With Anti-CD137 and Anti-PD1 Therapeutic Antibodies

Paolo A. Ascierto[a], Ester Simeone[a], Mario Sznol[b], Yang-Xin Fu[c], and Ignacio Melero[d]

Seminars in Oncology, Vol 37, No 5, October 2010, pp 508-516

Table 1. Anti-CD137 Clinical Studies

Status	Study	NTC Identifier	Phase	Condition
Terminated	A study of BMS-663513 administered in combination with chemotherapy to subjects with advanced solid malignancies	NCT00351325	Phase I	Advanced solid malignancies
Terminated	A study of BMS-663513 in combination with chemoradiation in subjects with non small cell lung carcinoma (NSCLC)	NCT00461110	Phase I/ phase II	NSCLC
Terminated	Study of BMS-663513 in patients with advanced cancer	NCT00309023	Phase I	Solid tumors
Withdrawn	Combination of anti-CD137 and ipilimumab in patients with melanoma	NCT00803374	Phase I	Melanoma
Completed	Phase II, second-line melanoma—RAND monotherapy	NCT00612664	Phase II	Melanoma

Ex

Ovarian Cancer

A Phase I Study on
T Cells for Ovarian

Michael H. Kershaw,[1,3,4] Jennif
Sharon A. Mavroukakis,[1] Donal
Clara C. Chen,[2] James C. Yang

Clin Cancer Res 2006;12(20)

Neuroblastoma

Antitumor activity and
T cells in patients with

Chrystal U. Louis,[1-3] Barbara Savo
Heidi V. Russell,[2,3] Oumar Diouf,[1]
Helen E. Heslop,[1,4] and Malcolm K

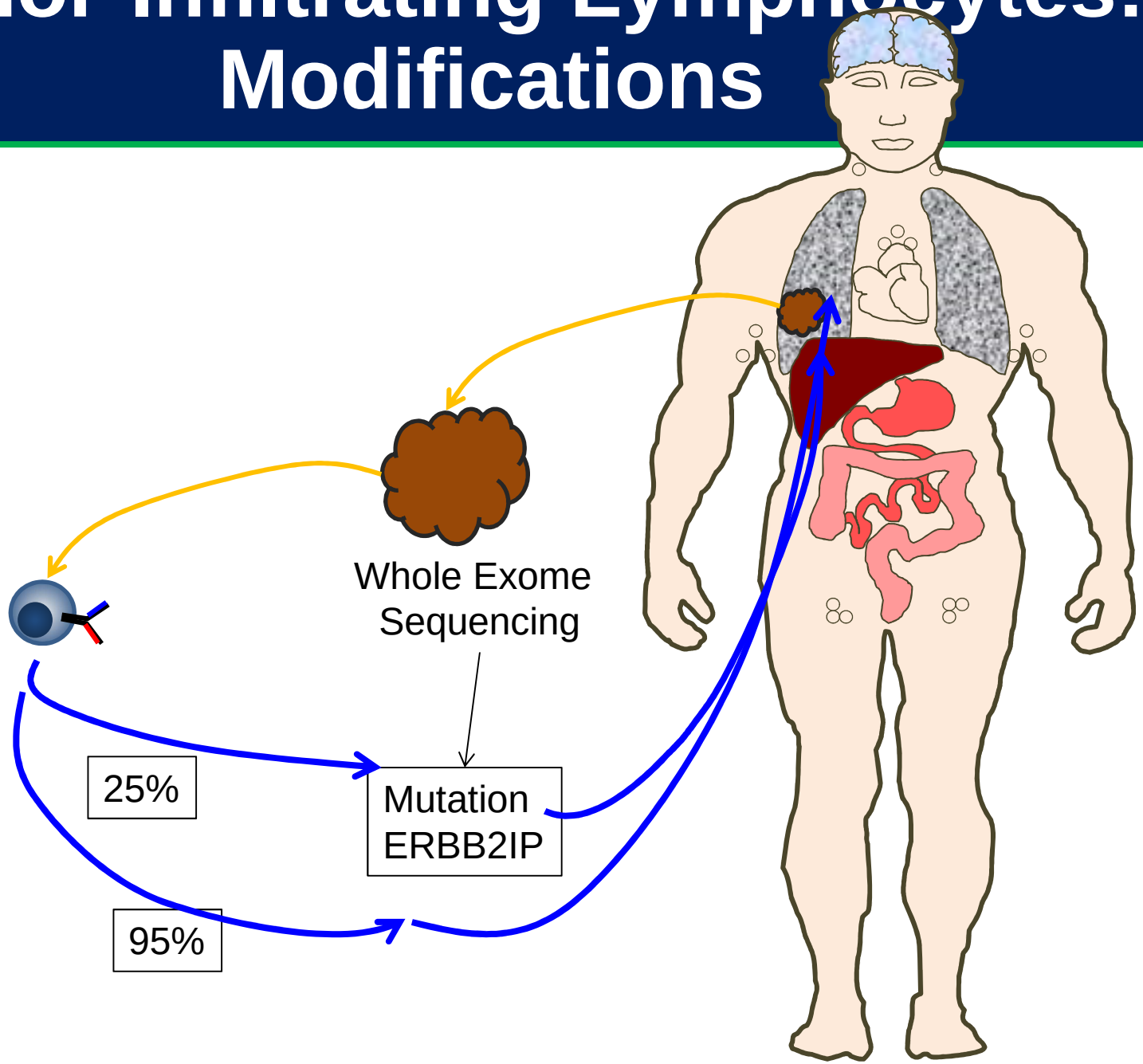
BLOOD, 1 DECEMBER 2011 • VOLUME 11

Natural Killer Cells

taNK (tumor-antig

Target	Cancers	Generation
A-folate receptor	Ovarian	1
CAIX	Renal	1,2
CD19	B-cell, CLL, B-ALL, follicular lymph,	1,2
CD20	B-cell, Mantle,	1,2,3
CD22	B-cell	2
CD30	Lymphoma, Hodgkin	1
CD33	AML	2
CD44v78	Cervical	2
CEA	Breast, Colon	1,2
EGP-2	Multiple	1
EGP-40	Colon	1
Erb-B2	Colon, Breast, meduloblastoma, glioblastoma, prostate, osteo	1,2
Erb-B2,3,4	Breast	1,2
FBP	Ovarian	1
Fetal acetylcholine R	Rhabdomyosarcoma	1
GD2	Neuroblastoma	1,3
GD3	Melanoma	1
IL-13R-a2	Glioblastoma, meduloblastoma	2
K-light chain	B-cell,	1,2
LeY	Carcinoma,	1,2
L1 CAM	Neuroblastoma	1
MAGE-A1	Melanoma	2
Mesothin	Various	2,3
MUC1	Breast, ovary	3
NKG2D ligands	Various	1

Tumor-Infiltrating Lymphocytes: Modifications



Challenge: Interleukin-2

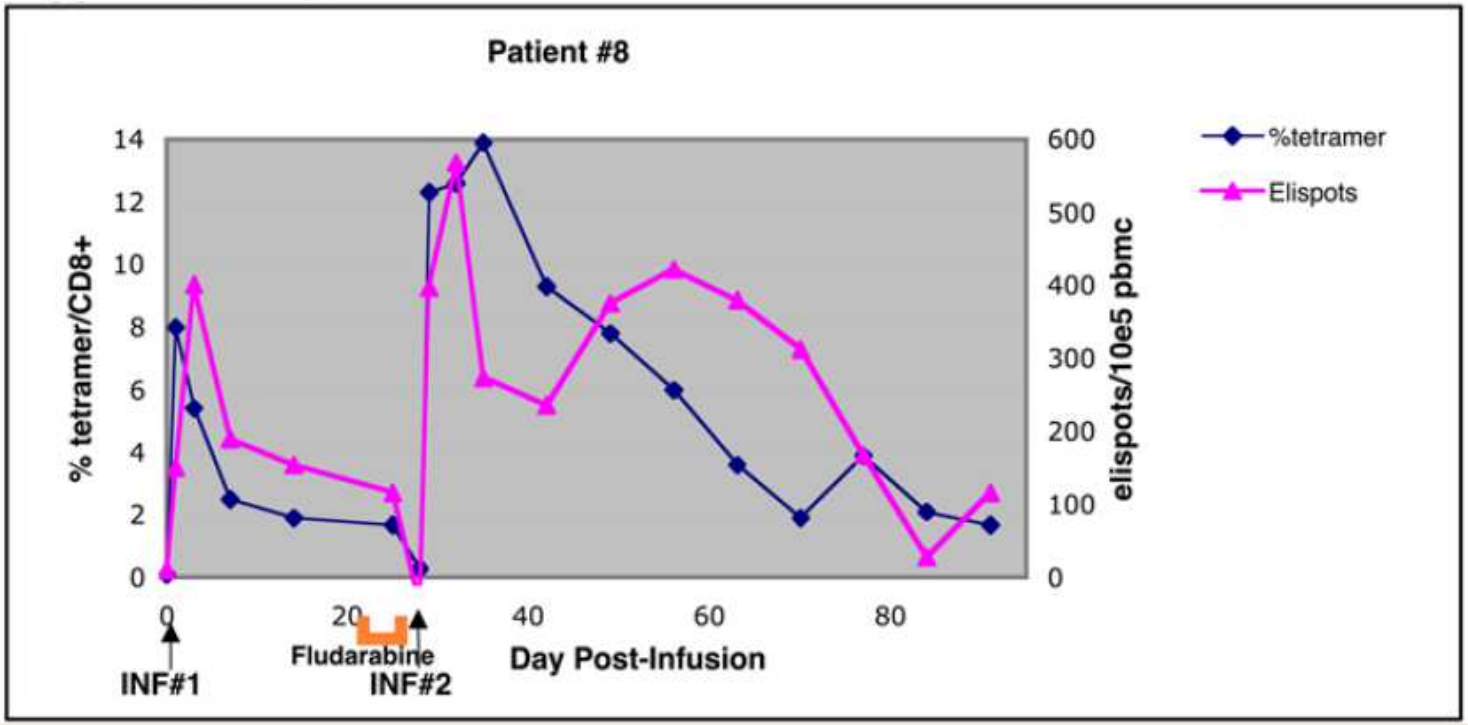
- High-dose IL-2
  - Toxic/stressful
- Lower dose IL-2?
- Combine with or substitute checkpoint inhibition?

Lymphodepletion

Fludarabine Modulates Immune Response and Extends *In Vivo* Survival of Adoptively Transferred CD8 T Cells in Patients with Metastatic Melanoma

Herschel Wallen*, John A. Thompson, J. Zachary Reilly, Rebecca M. Rodmyre, Jianhong Cao, Cassian Yee

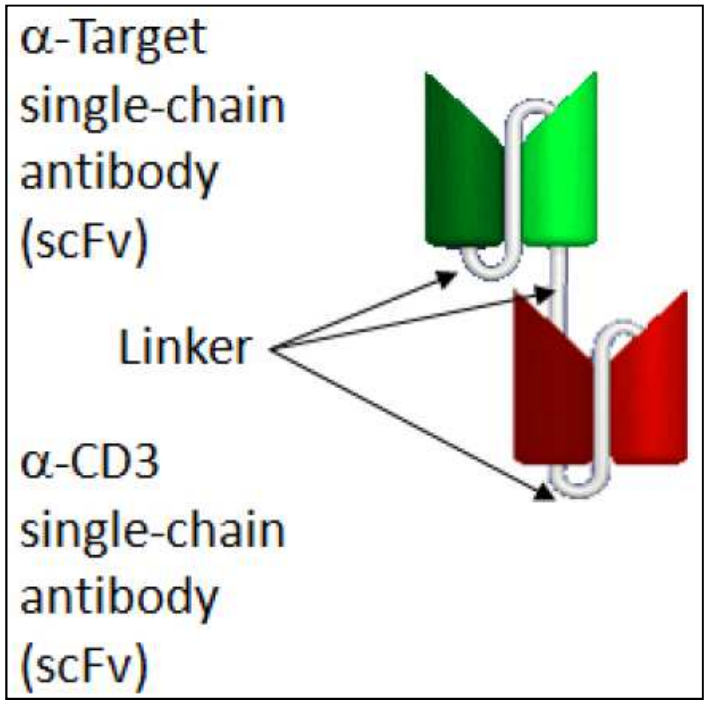
March 2009 | Volume 4 | Issue 3 | e4749



Cells given with no IL-2 or low-dose IL-2

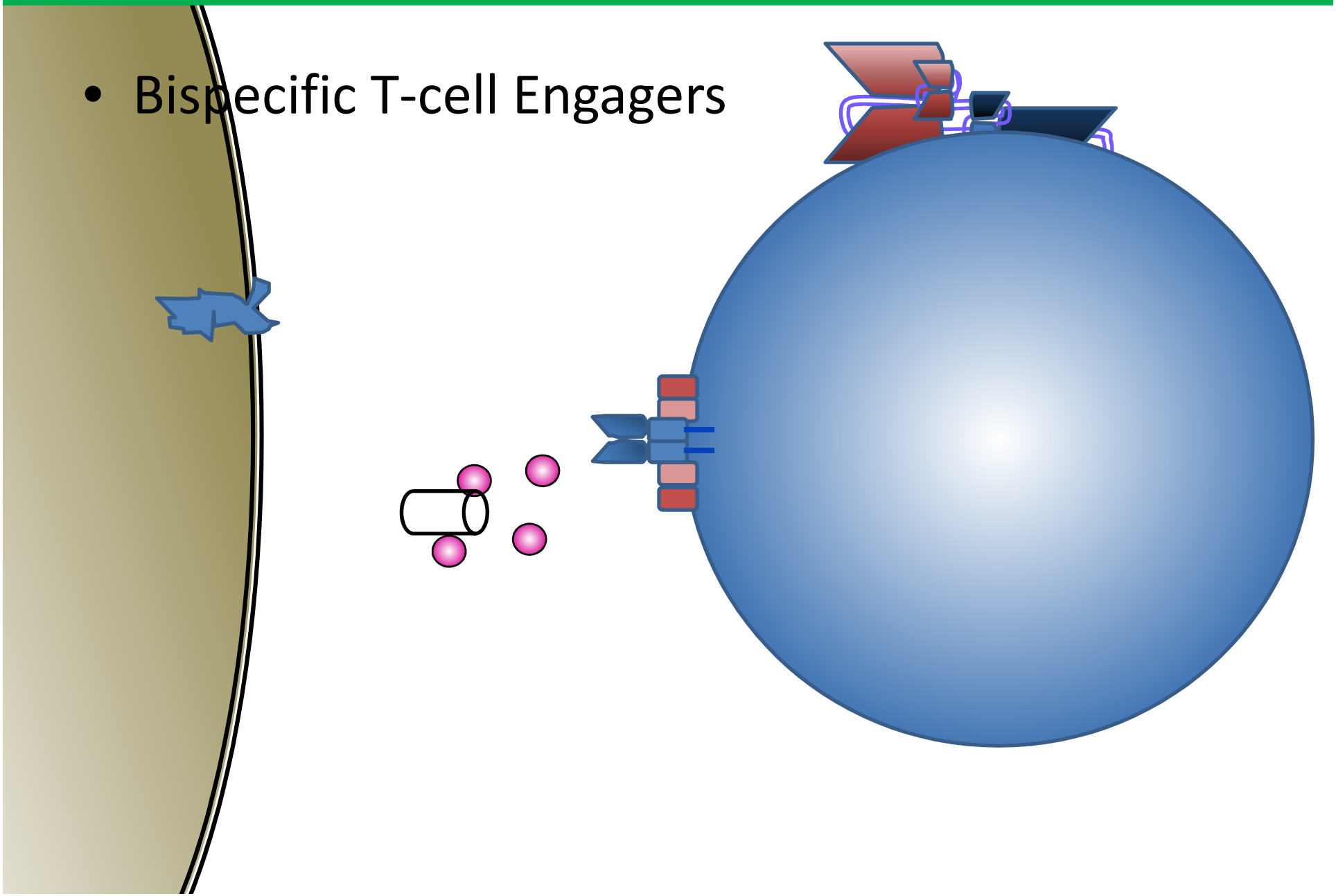
Bispecifics

- BiTE: Bispecific T-cell Engagers
  - Variable heavy/light chain with short linker
  - Specific for: - CD3 on one end
    - tumor antigen on the other
  - CD19, Her2/neu, EpCAM
  - Blinatumomab (CD3/CD19)
    - Approved Dec 3, 2014
    - 11% neurologic toxicity
  - IMCgp100 in melanoma
    - 17 patients (AACR)
    - 4 CR/PR



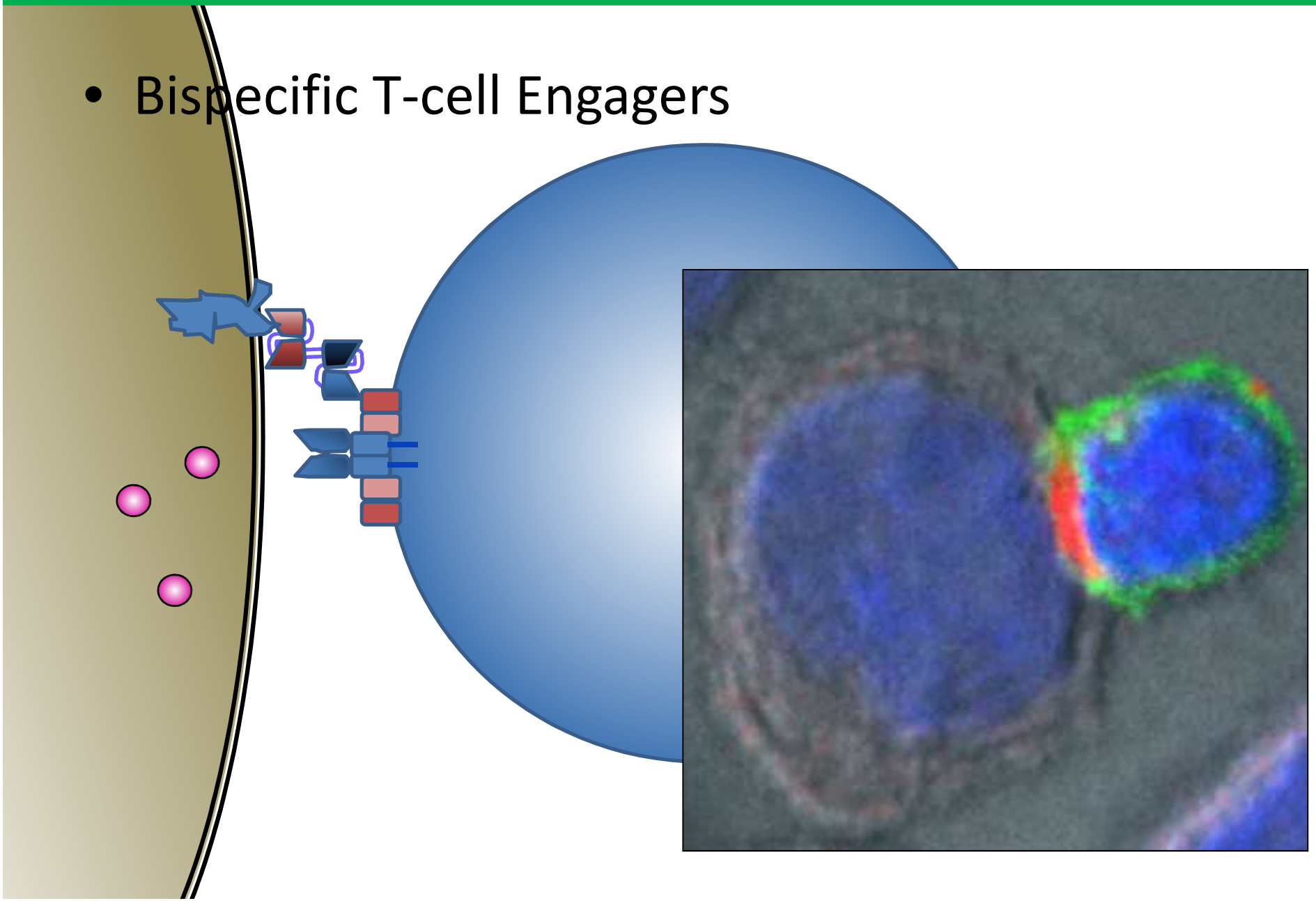
BiTE

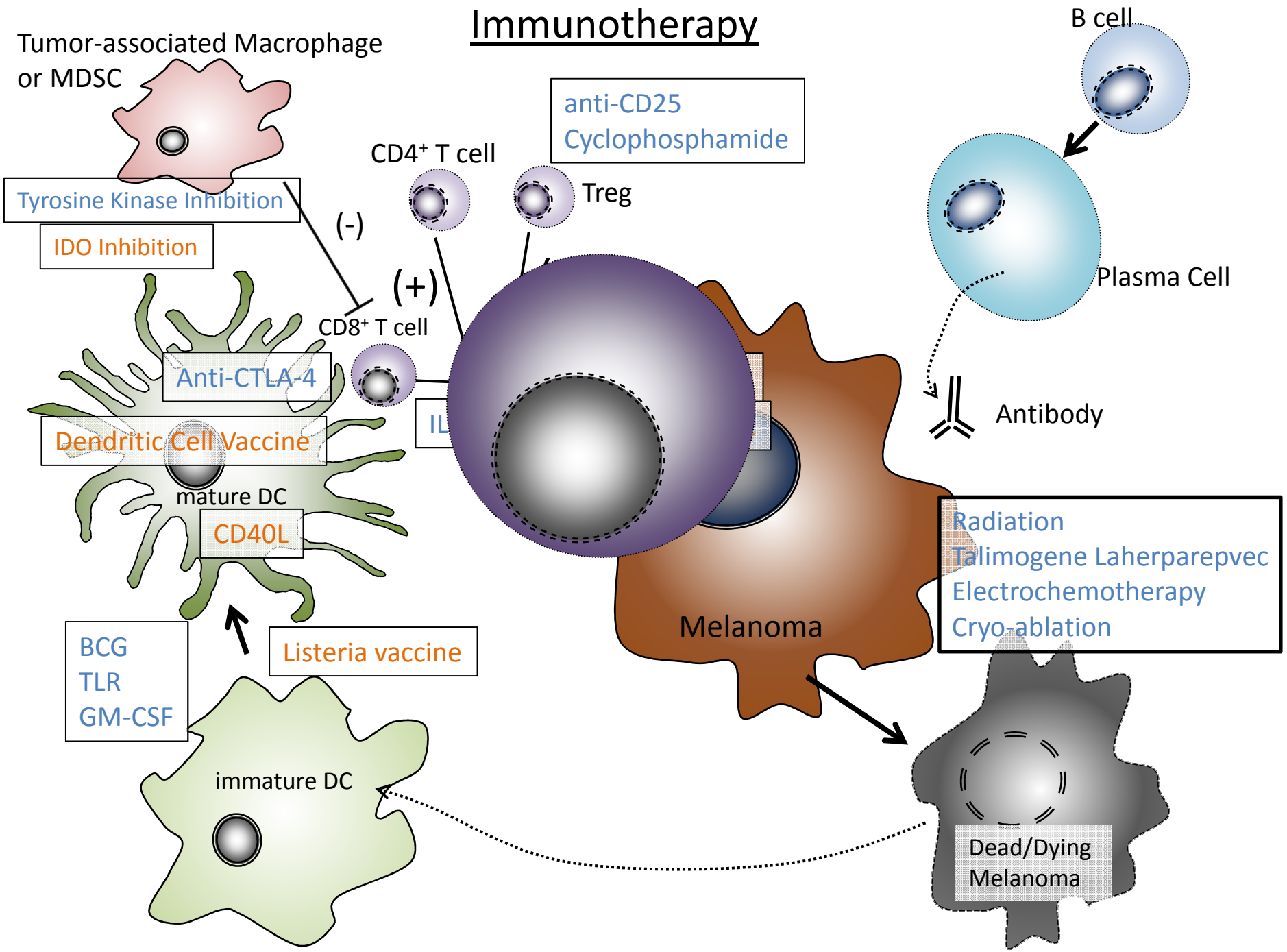
- Bispecific T-cell Engagers



BiTE

- Bispecific T-cell Engagers




Immunotherapy
Tumor-associated Macrophage or MDSC
Tyrosine Kinase Inhibition
IDO Inhibition
(-)
CD4+ T cell
Treg
anti-CD25
Cyclophosphamide
B cell
Plasma Cell
Antibody
(+)
CD8+ T cell
Anti-CTLA-4
IL
Dendritic Cell Vaccine
mature DC
CD40L
Radiation
Talimogene Laherparepvec
Electrochemotherapy
Cryo-ablation
Melanoma
BCG
TLR
GM-CSF
Listeria vaccine
immature DC
Dead/Dying Melanoma


Thank You
JOHN WAYNE
CANCER INSTITUTE
at Saint John's Health Center