

ANTIGENS AND TOXICITY WITH DESIGNER T CELLS

Under FDA/OBA: CEA, PSMA

Foreign experience: G250, CEA, CD19, LeY

Richard P Junghans, PhD, MD

Director, Biotherapeutics Development Lab
Associate Professor of Surgery and Medicine
Boston University School of Medicine
Chief, Division of Surgical Research
Roger Williams Medical Center
Providence, RI, USA

No commercial relationships to disclose.

Antigens

- o Carcinoembryonic antigen (CEA)
- o Prostate specific membrane antigen (PSMA)

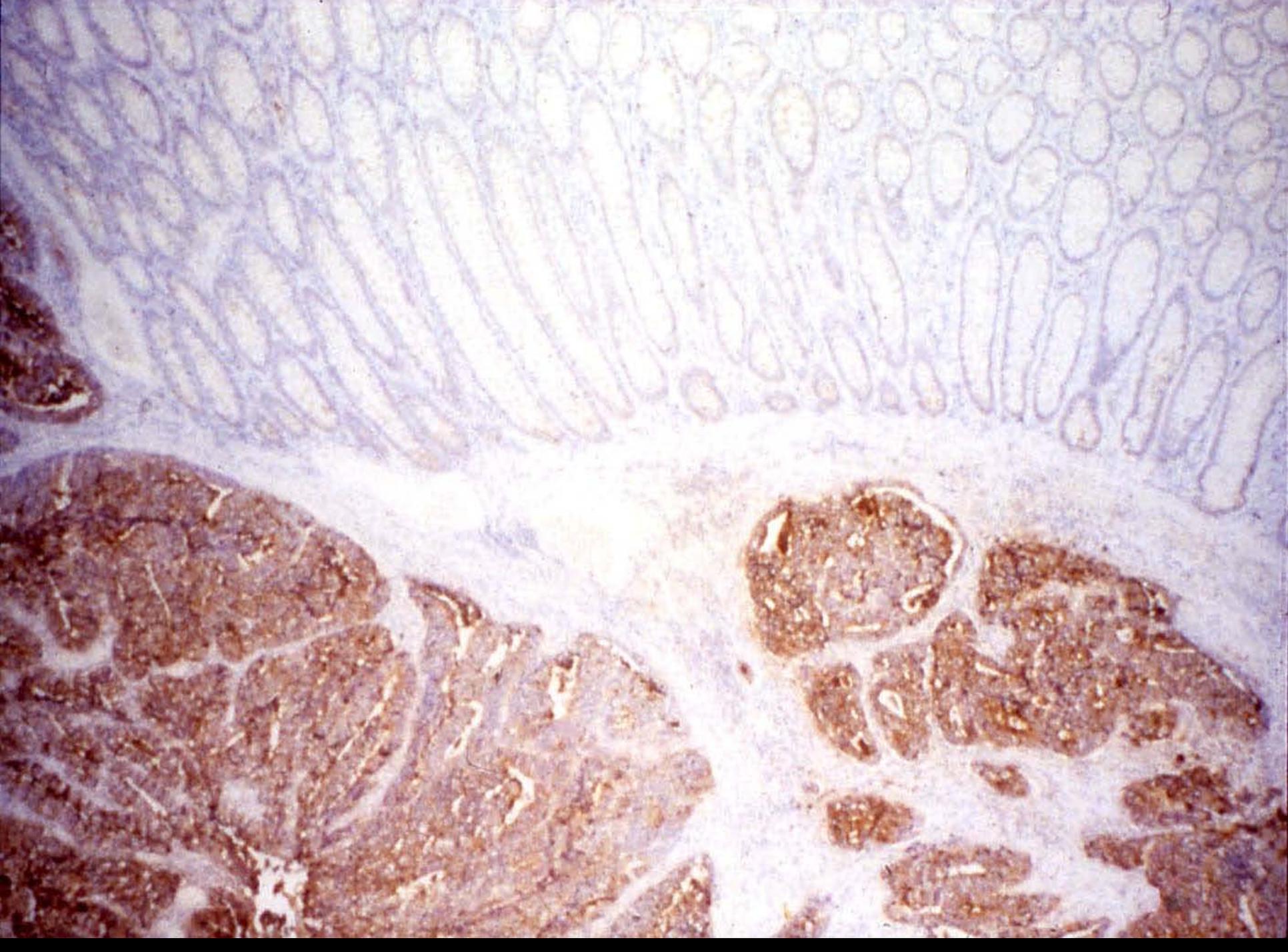
- o Foreign experience
 - G250 (Lamers)
 - CEA (Hawkins)
 - CD19 (Hawkins)
 - Lewis y (Le-y) (Kershaw)

Study Types

ANTIGEN	GEN	MODE	STRATEGY	IL2
CEA (US)	1	INFUSE	1	-IL2/+IL2
CEA (UK)	1	ENGRAFT	2	+IL2
CEA (US)	2	INFUSE	3	-IL2
CAIX (ND)	1	INFUSE	1	-IL2
PSMA (US)	1	ENGRAFT	2	+IL2
CD19 (UK)	1	ENGRAFT	2	+IL2
Lewis-Y (AU)	2	ENGRAFT	4	-IL2

Carcinoembryonic antigen (CEA)

- o Expression
 - High on tumor, low on normal
 - Topological sequestration
- o High clinical relevance:
 - On colorectal, breast, pancreas, lung, others
 - More than 100,000 deaths/yr for CEA+ tumors



CLINICAL TRIAL

Clinical Data: 1st Generation

Phase I Study of Anti-CEA Designer T Cells in Adenocarcinoma ("1st generation")

FDA BB IND

7301

Strategy 1: 1st gen infused

Clinical Summary

- o Number of doses administered (24)
- o Patients treated (7): 5 colorectal, 2 breast
- o Doses sizes administered
 - 1×10^9 , 3×10^9 , 1×10^{10} , 3×10^{10} , 1×10^{11} cells

Pharmacodynamics

- o Immunogenicity: None.
 - 0/7 with plasma reactivity against designer T cells
- o IL2 arm: Systemically active.
 - Positive for NK cell expansion, T cells stable

Toxicity

- o “Probably related” or “Definitely related”
 - No grade III toxicity, one grade IV toxicity (grade II fever >> grade IV SVT)
 - No delayed grade III, IV toxicity
 - Positive for low grade fevers, mild GI symptoms (<grade III)
 - Transient hypoxemia (O_2 sat<90%) with high T cell dose

Toxicity

(-) IL 2

Name	Sex	Age	Diagnosis	Dose	Fever (24h)	Adverse Events (Grade III-IV)	Relatedness
MS Dose 1 (6/10/98) Dose 2 (6/24/98) Dose 3 (7/8/98)	F	75	Colon Ca	1x10 ⁹ 3x10 ⁹ 1x10 ¹⁰	- 102.3 F	↑ Bilirubin GI Bleed * Death *	Possibly (temporal only) [#] Possibly (temporal only) [#]
RH Dose 1 (7/13/99) Dose 2 (7/27/98) Dose 3 (8/10/98) Dose 4 (8/26/98)	M	55	Rectal Ca	1x10 ⁹ 3x10 ⁹ 1x10 ¹⁰ 3x10 ¹⁰	102 F 101 F <101 F <101 F	Anemia	Possibly (temporal only) [#]
DB Dose 1 (7/15/98) Dose 2 (7/29/98) Dose 3 (8/12/98) Dose 4 (8/26/98)	M	54	Colon Ca	1x10 ⁹ 3x10 ⁹ 1x10 ¹⁰ 3x10 ¹⁰	99.8 F Rigors 102.1 F	↑ Bilirubin (9/23/98;28 days)	Possibly (temporal only) [#]
HF Dose 1 (8/11/98) Dose 2 (8/25/98) Dose 3 (9/14/98) Dose 4 (10/14/98) Dose 5 (2/1/99)	M	75	Colon Ca	1x10 ¹⁰ 3x10 ¹⁰ 1x10 ¹¹ 1x10 ¹¹ 1x10 ¹¹	- - - - -	A Flutter* A Flutter Death * (2/3/99)	Possibly (temporal only) Possibly (temporal only) [#]
GT Dose 1 (6/8/99)	M	69	Rectal Ca	1x10 ¹¹	103.8 F	SVT/Hypotension* Rigors	Probably (to fever)

(+) IL 2

Name	Sex	Age	Diagnosis	Dose	Fever (24H)	Adverse Events (Grade III-IV)	Relatedness
JD Dose 1 (9/23/98) Dose 2 (10/5/98) Dose 3 (10/19/98) Dose 4 (11/2/98)	F	39	Breast CA	1x10 ⁹ 3x10 ⁹ 1x10 ¹⁰ 3x10 ¹⁰	102 F 102 F		
EM Dose 1 (11/4/98) Dose 2 (11/16/98) Dose 3 (11/30/98)	F	47	Breast CA	1x10 ⁹ 3x10 ⁹ 1x10 ¹⁰	101.2 F	↑ Bilirubin Death*	Possibly (temporal only) [#] Possibly (temporal only) [#]

* Event generating SAE report

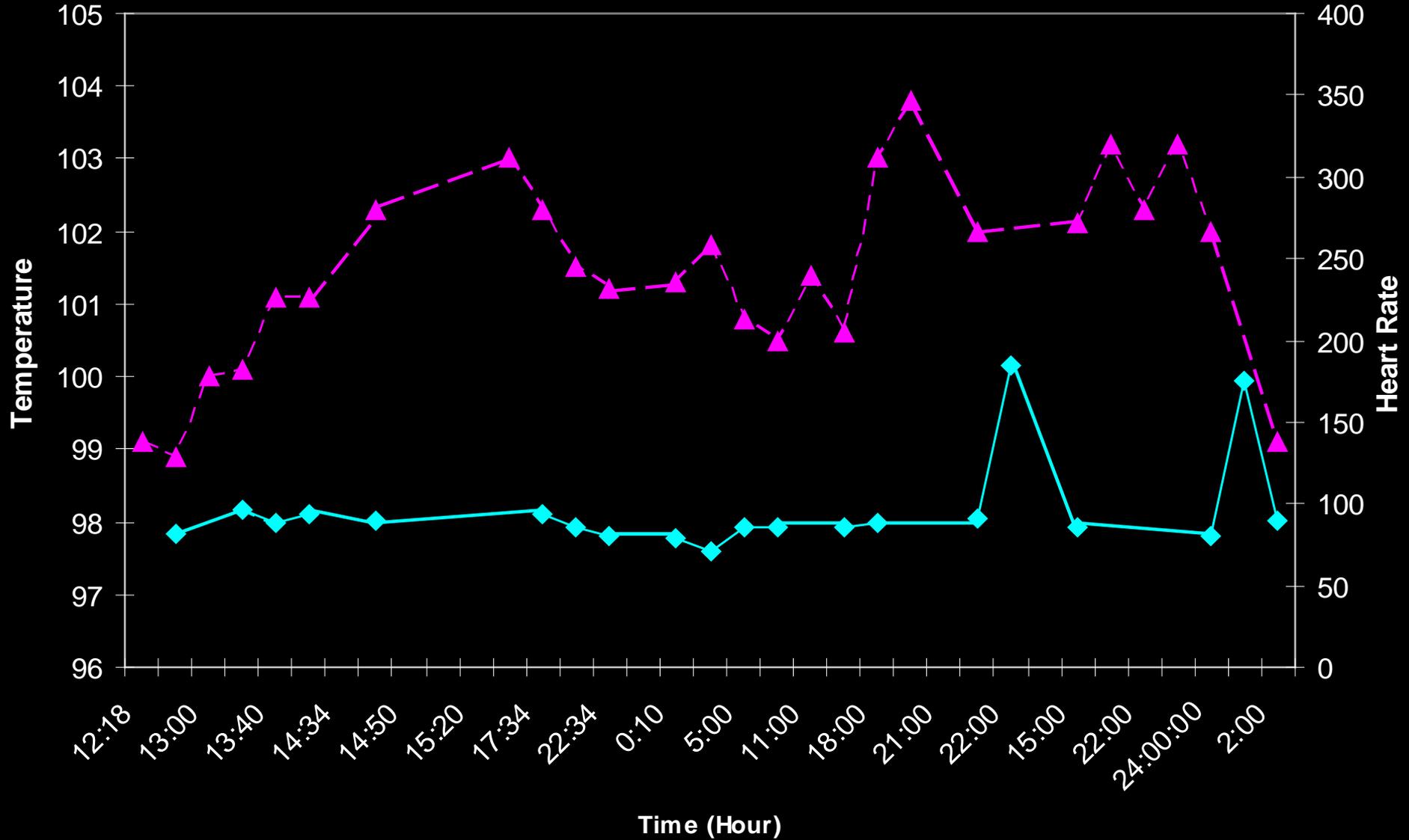
Current progression

Patient GT

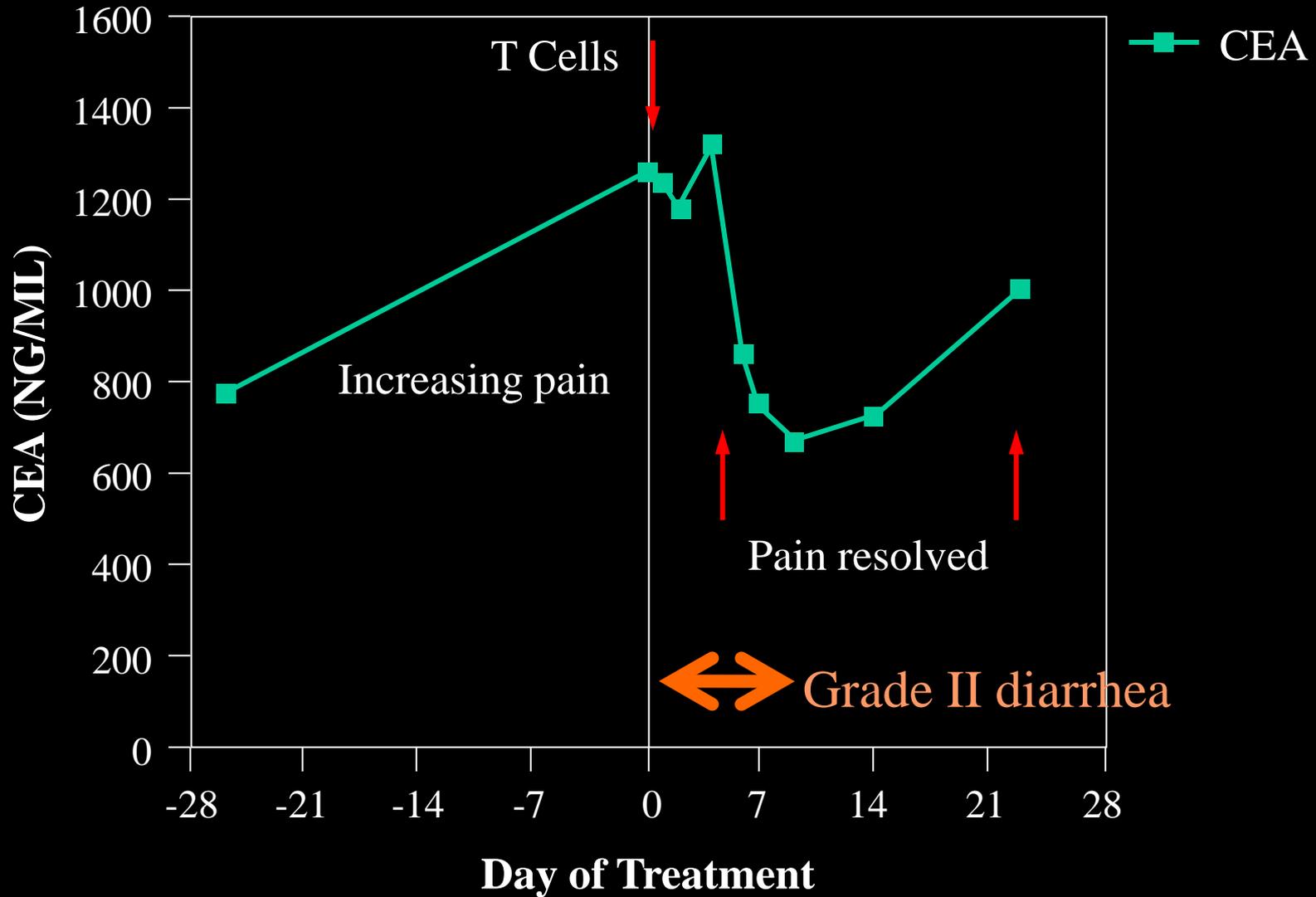
- o 69M, rectal ca, baseline RBBB
 - Febrile 103.8F (39.9C) within 6 hrs
 - SVT, responsive to IV beta blockers
 - blood pressure, 20 mm drop
 - asymptomatic
- o blood cultures neg, cell cultures neg
- o expect it: >>immune response indicators
 - recommend as pharmacodynamic measure
- o avoid predisposing cardiac conditions
- o Grade II diarrhea (negative for blood)

GT Vital Signs

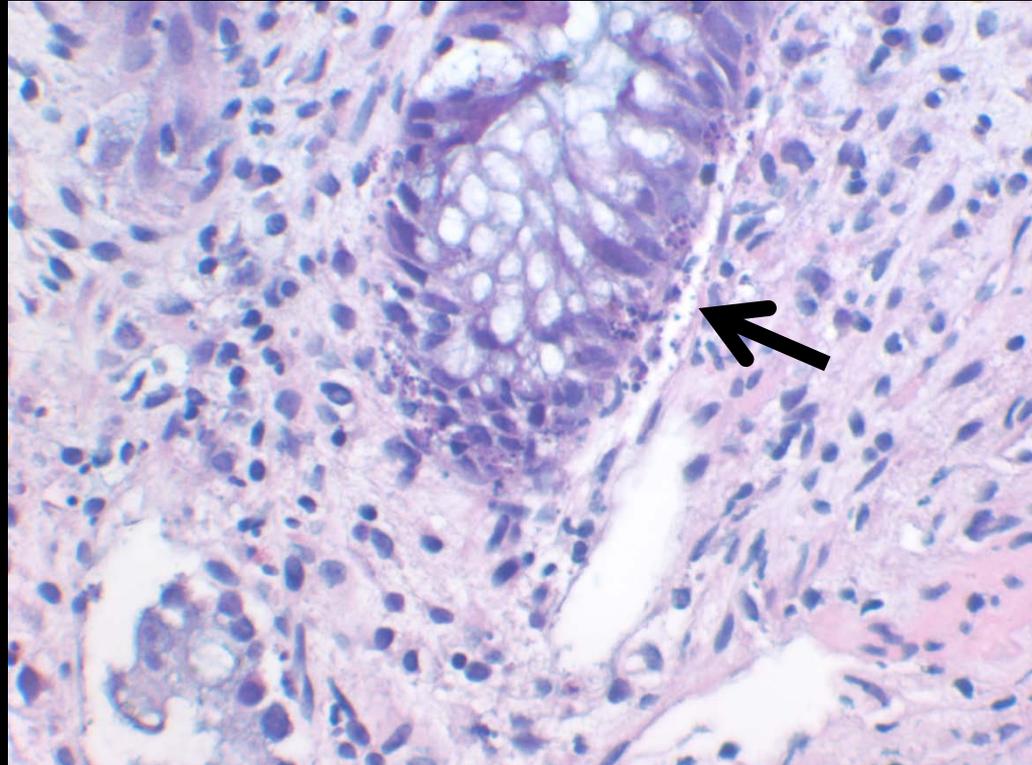
- Temperature
- Heart Rate



Patient Response

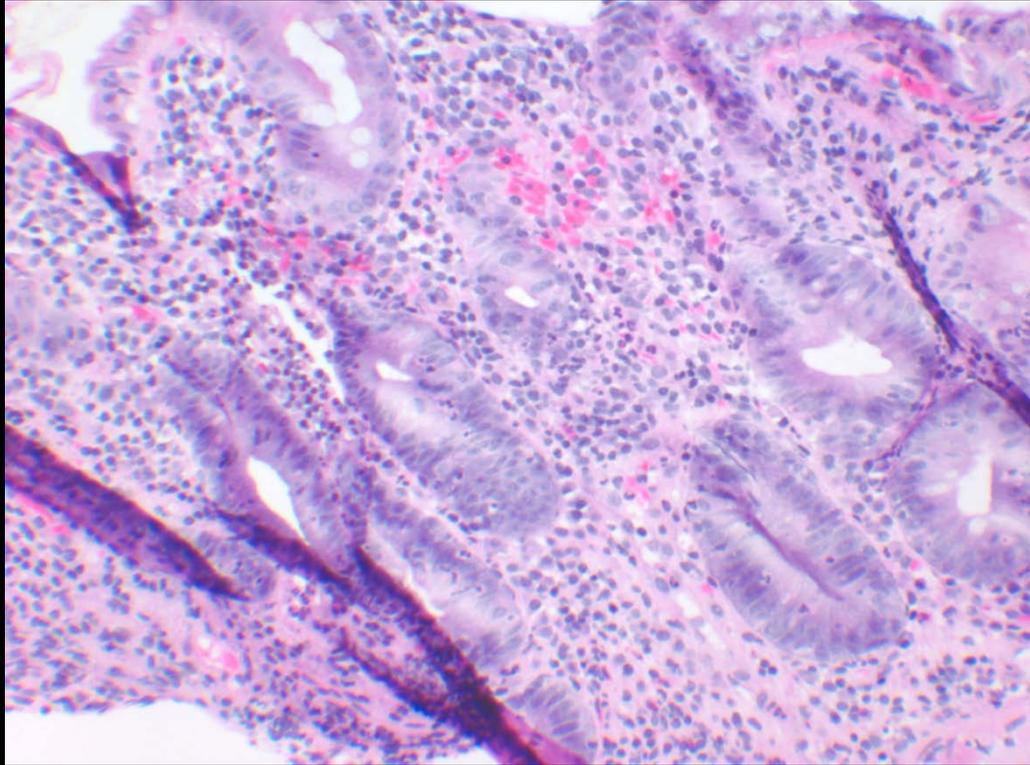


GVHD in bowel



Apoptotic bodies at base
of crypts

GT biopsy:
no apoptotic bodies



Conclude: cytokine syndrome

Phase Ia/Ib Trial of 2nd Generation
Anti-CEA Designer T Cells in
Adenocarcinoma

FDA BB IND
10791

Strategy 3: 2nd gen infused

Escalation Plan

T Cell Dose, Number of Cells

Pt #	Cohort	-IL2		+IL2	
		<u>1x10⁹</u>	<u>1x10¹⁰</u>	<u>1x10¹¹</u>	<u>1x10¹¹</u>
#1		X			
#2	I	X			
#3		X			
#4					X
#5	II		X		
#6				X	
#7					X
#8	III			X	
#9				X	
Completes Phase Ia goals (-IL2)					
#10				(Bx) X	
#11				X	
#12	R IV			X	
#13	A			X	
#14	N			X	
#15	D			X	
	O				(Bx)
#16	M				X
#17	I				X
#18	Z V				X
#19	E				X
#20					X
#21					X
Completes Phase Ib goals (OBD -IL2/+IL2)					

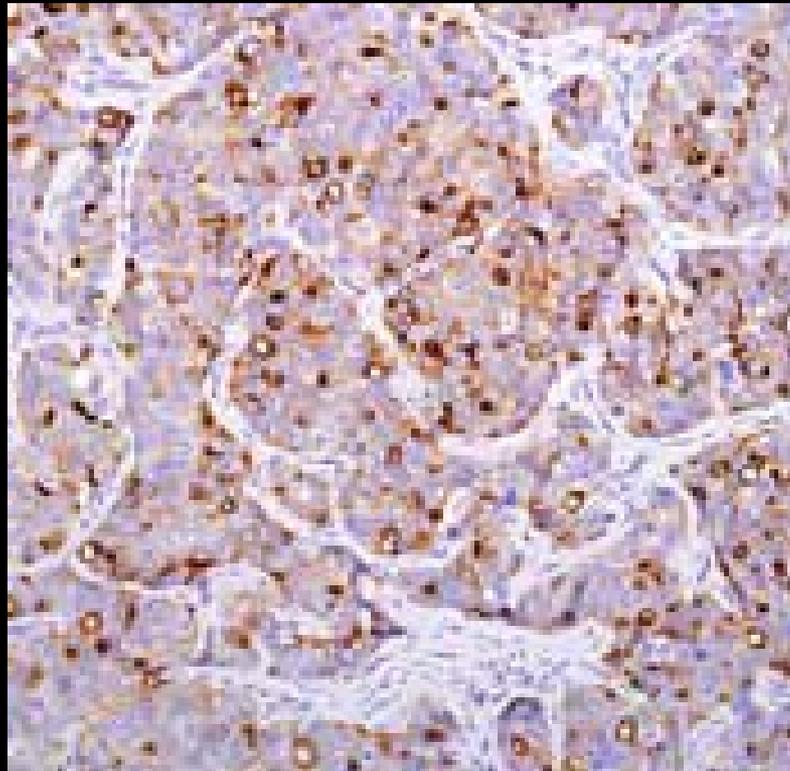
Summary 2nd Generation CEA

- o 5 patients treated
 - 1st cohort completed (10^9 cells)
 - 2nd cohort in process (10^{10} cells)
- o Safety, no SAEs (no new risks with 2nd gen)
- o Responses
 - one “minor” (brain and lung)
 - one SD 12+ months
- o Continue in escalation
- o Need to assess value of IL2 supplementation

Prostate Specific Membrane Antigen (PSMA)

- o Surface membrane glycoprotein 100,000 Daltons
- o Unrelated to PSA
- o Normal prostate epithelium and vasculature
 - (reportedly on type II astrocytes?)
- o Elevated expression in metastatic lesions and hormone refractory disease
- o High clinical relevance:
 - 28,000 deaths per year from PSMA+ prostate tumors
- o Antibody (3D8) from G. Murphy and A. Boynton

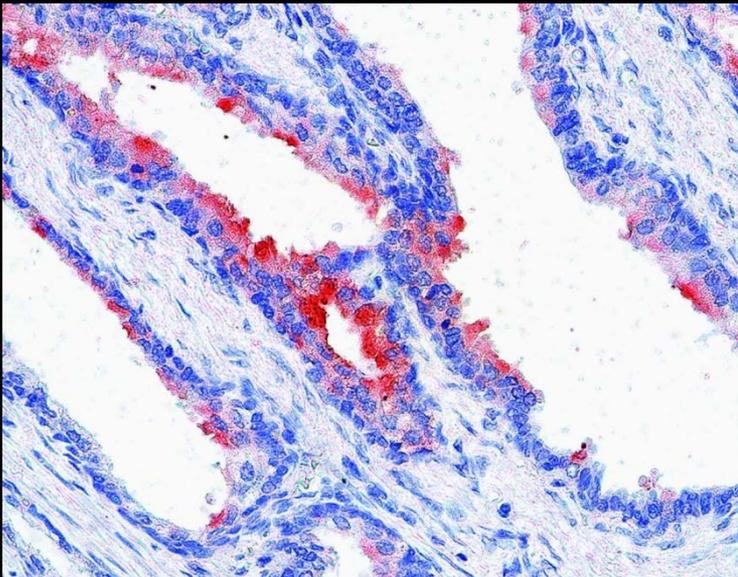
PSMA on prostate cancer



Normal tissue PSMA

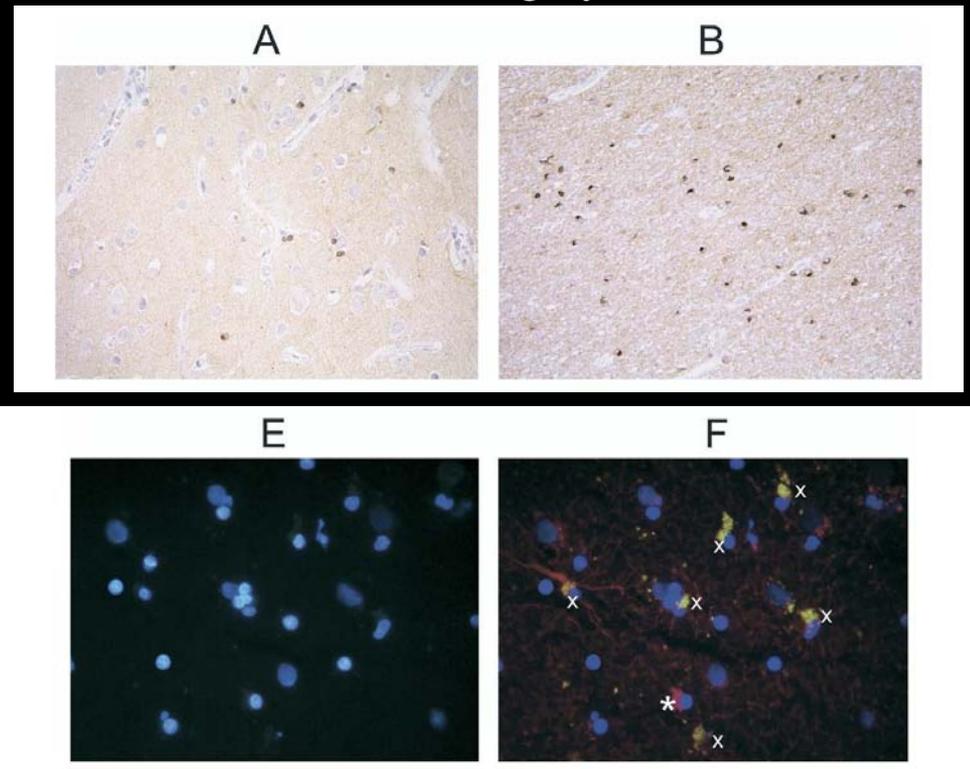
Tasch et al. Crit Rev
Immunol 2001

Prostatic
epithelium and
vasculature –
“Dispensable”



Type II
astrocytes

white gray



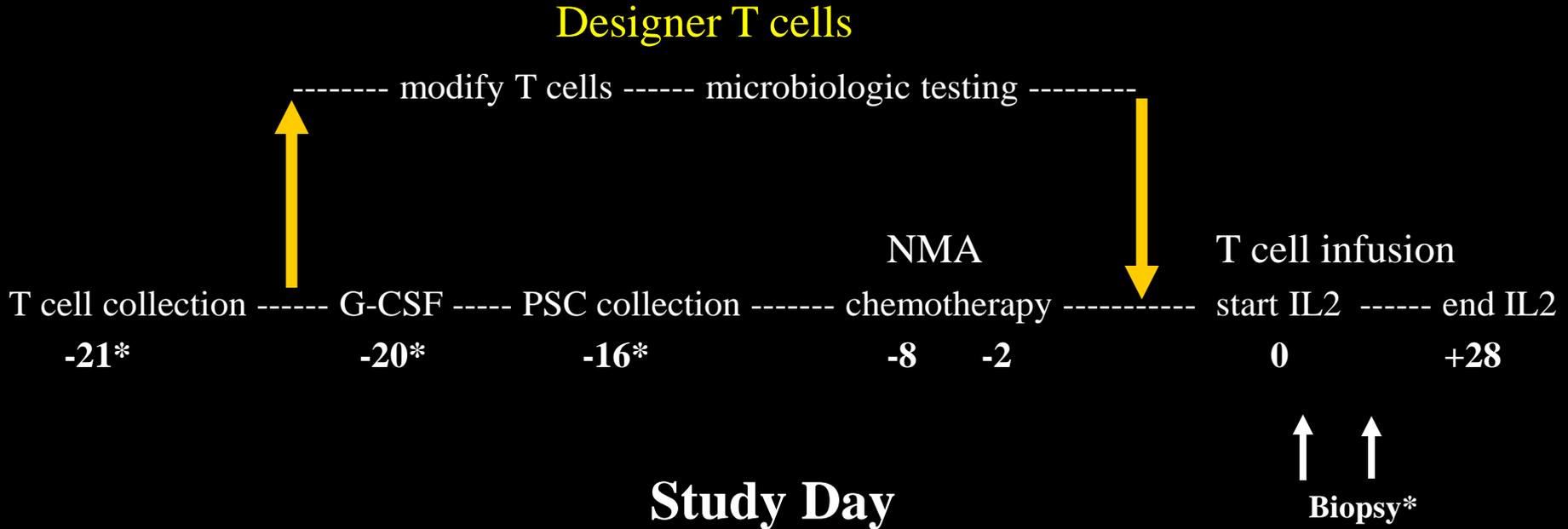
And brain??!

Kinoshita et al. W J Surg 2006
Sacha et al. Neuroscience 2007

Phase I Study of Autologous
Transplantation of Anti-PSMA
Designer T Cells after NMA
Conditioning in Prostate Cancer

BB IND 12084

Treatment Schema



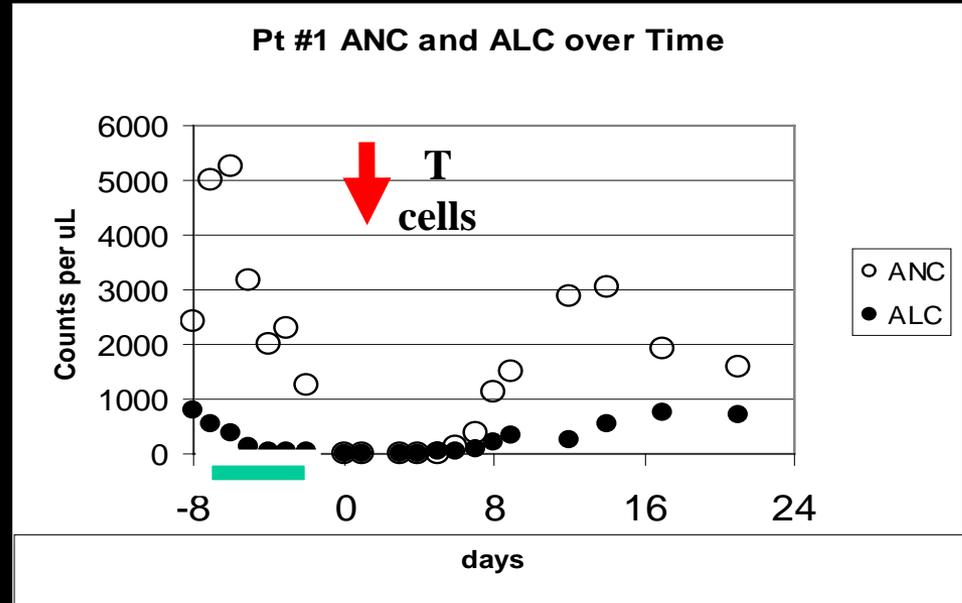
CTX 60 mg/kg d-7, d-6
Fludarabine 25 mg/m² d-5 to d-1

Phase I Study Enrollment Plan

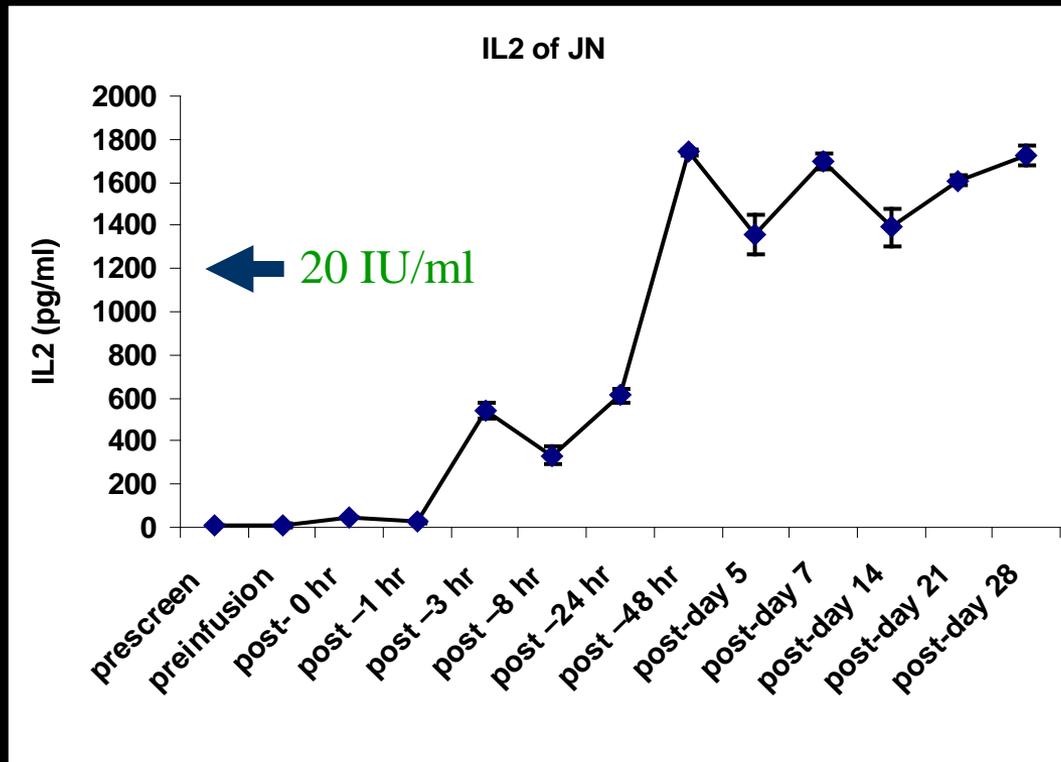
		T Cell Dose, Number of Cells		
Pt #	Cohort	10.9	10.10	10.11
#1	I	X		
#2		X		
#3		X		
#4		X		
#5		X		
#6		X		
#7	II		X	
#8			X	
#9			X	
#10			X	
#11			X	
#12			X	
				(Bx)
#13	III			X
#14				X
#15				X
#16				X
#17				X
#18				X

Peripheral Blood Recovery

- o Chemo d-8 to d-2
- o T cells d0
- o IL2 start d0-d28
- o ANC=0 x5-8 d
 - Recovery ANC>500



IL2 via Continuous Infusion



75,000 IU/kg/d

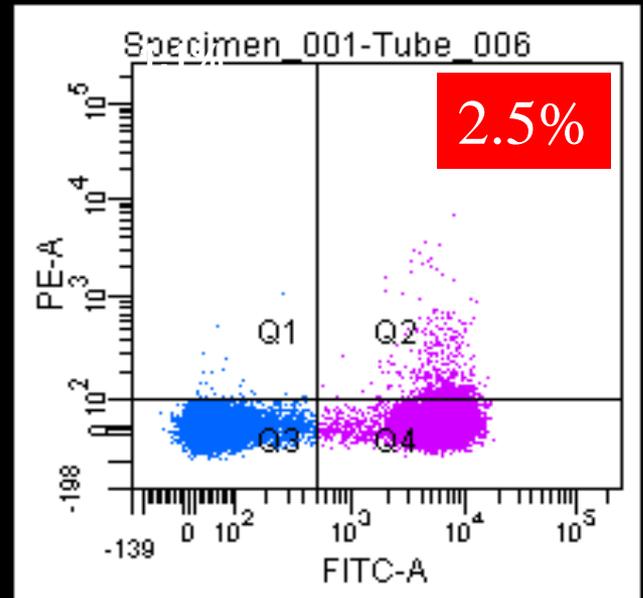
~ 3 MIU/m²/d

Engraftment

Blood sample #1

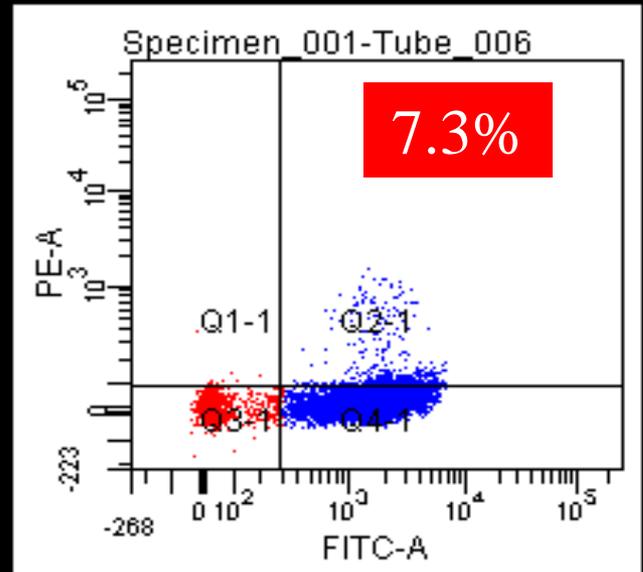
Day +14

CIR+

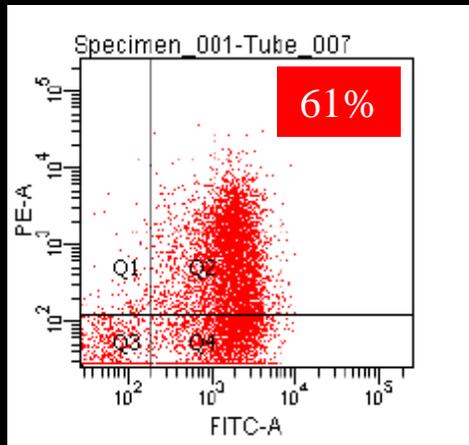


#2

CIR+



Dose



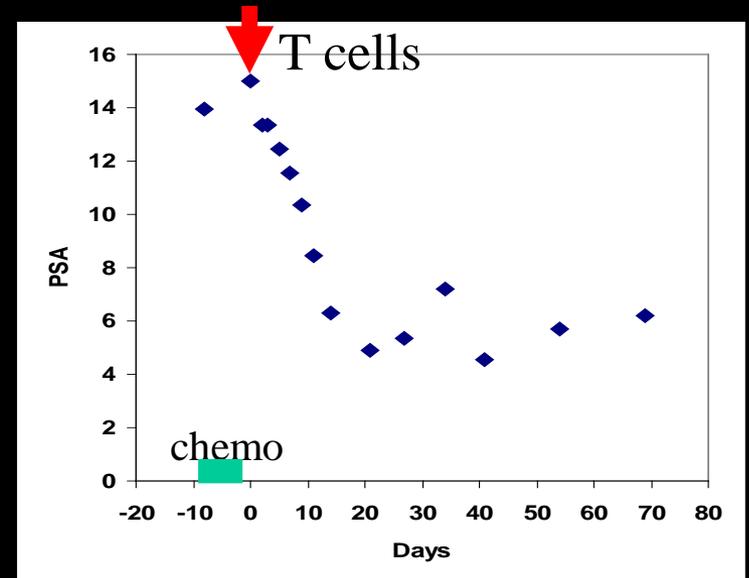
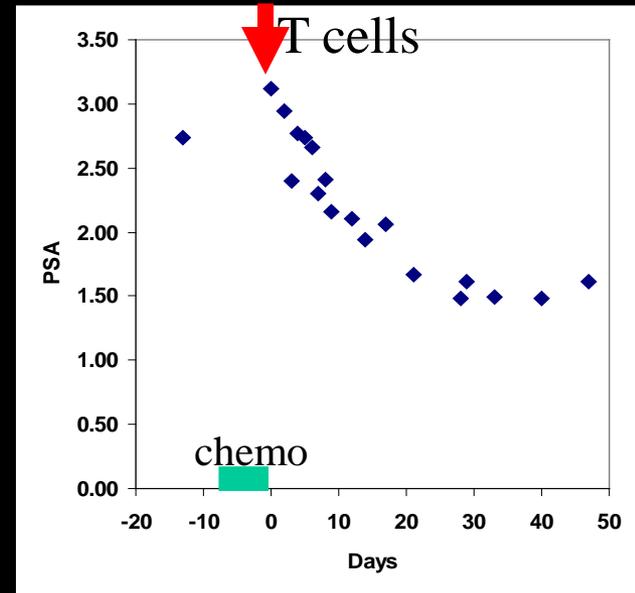
CD3+

PSA Response

Conditioning d-8 to d-2

T cells infused d0

Low dose IL2 d0 to d28+



Summary Prostate

- o Five patients treated
 - 10^9 cells (3), 10^{10} cells (2)
 - Safely administered; toxicity due to conditioning
 - Neutropenic fevers, hospitalization for antibiotics
 - Malaise, fatigue (IL2)
 - 50 and 70% reduction in PSA in two subjects
- o More doses to follow in escalation
 - 10^{10}
 - 10^{11}
- o **Limitations???**
 - 1st generation: signal 1 only,
 - After resting, do not reactivate
 - 2nd generation in preclinical
- o Conclude: PSMA “safe” for DTC targeting

Foreign experience

- o G250 (Lamers)
- o CEA (Hawkins)
- o CD19 (Hawkins)
- o Lewis y (Le-y) (Kershaw)

Engineered T Cell Therapy

Trials in Melbourne

Michael H. Kershaw, PhD

Laboratory Head

Cancer Immunotherapy Research

Peter MacCallum Cancer Centre

East Melbourne, Victoria 3002

Australia

A phase I study investigating the tolerability, safety and biological parameters of an infusion of autologous peripheral blood T lymphocytes transduced with an anti-LewisY chimeric receptor gene in patients with LewisY positive multiple myeloma.

The Lewis^Y antigen

- A carbohydrate moiety on undefined proteins
- Associated with 30-90% of human carcinomas, including lung, breast, colon, ovarian, prostate
- Approximately 20% of AML and multiple myeloma
- Also expressed on some normal cells of:
 - Esophagus
 - Stomach and intestine
 - Exocrine cells of pancreas
 - Some epithelial cells in gallbladder
 - Ciliated epithelium of the trachea and bronchus
 - Type II pneumocytes
 - Neutrophils
- Expression on normal tissues lower than on tumors, confined to luminal side of tissue
- Safely targeted in Ab therapy, with localization of ¹¹¹In label

Details of first two Lewis-Y⁺ patients

	Patient 1	Patient 2
Disease	Acute myeloid leukemia	Acute myeloid leukemia
Conditioning	Chemotherapy (Fludarabine 25/m ² x2d)	Chemotherapy (Fludarabine 25/m ² x2d)
T cell dose	5 x 10 ⁸ No IL2	1 x 10 ⁹ No IL2
Engraftment	Detected at 3w (PCR)	Detected at 3w (PCR)
Adverse events	None	None
Response	None	None

T cells homing in on target

