

Innate Core and Adaptive Shell

Cytokine-based immunotherapies and other molecular bispecifics, other immunotherapies

Michael T. Lotze, MD—*Nurix Therapeutics, Chief Cellular Therapy Officer San Francisco and Pittsburgh*

- TNF and IL-1/FGF/HMGB1 Family Members (Leaderless cytokines)
- The Interferons, IL-10 Family
- IL-2 Family Members
- IL-12 Family Members
- Pegylated or Muteinized Cytokines
- Anti-cytokines (TNF, IL-17, etc.)
- Cytokine-antibody conjugates



Disclosures-Company & Consultant

- **Clinigen (IL-2)**
- **Nurix (NextACT) Chief Cellular Therapy Officer**
- **Checkmate, Inc.**
- **iRepertoire, Inc. (Hudson Alpha Institute)**

Before we begin, I would like to remind you that my comments and responses to questions reflect my views only and are not necessarily those of Nurix, Nurix's management team or Nurix's board of directors.

Moreover, my comments and responses are made only as of today, and may include statements related to Nurix, Nurix's product candidates and Nurix's business that are forward-looking statements under the federal securities laws. Actual results may differ materially from those contained in or implied by these forward-looking statements due to risks and uncertainties associated with Nurix's business. For a discussion of the material risks and other important factors that could impact Nurix's actual results, please refer to Nurix's SEC filings, which can be found on the Nurix website.

Finally, any statements I may make about Nurix, Nurix's product candidates and Nurix's business are not intended to contradict or modify Nurix's existing public disclosures.

Cytokines (1728) and Bispecific (216) Clinical Trials for Cancer clinicaltrials.gov

Showing: 1-100 of 216 studies 100 studies per page Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Study of Activated Cytokine-induced Killer Armed With Bispecific Antibody for Advanced Liver Cancer	• Advanced Liver Cancer	• Biological: Activated CIK and CD3-MUC1 Bispecific Antibody in Treating Liver Cancer • Procedure: cryotherapy	• Biological treatment center in Fuda cancer hospital Guangzhou, Guangdong, China • Institutional Review Board of Guangzhou Fuda Cancer Hospital Guangzhou, Guangdong, China
2	☐	Recruiting	Study of Activated Cytokine-induced Killer Armed With Bispecific Antibody for Advanced Breast Cancer	• Advanced Breast Cancer	• Biological: Activated CIK and	• Institutional Review Board of Guangzhou

<https://www.fda.gov/media/123313/download> Activating and non-activating (The minimum anticipated biological effect level-MABEL dose)

Showing: 1-100 of 1,728 studies 100 studies per page Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	Radiofrequency Ablation Combined With Cytokine-induced Killer Cells for Colorectal Cancer Liver Metastases	• Colorectal Cancer	• Procedure: Radiofrequency ablation • Biological: Cytokine -induced killer cells	• The First People's Hospital of Changzhou Changzhou, Jiangsu, China
2	☐	Active, not recruiting	ELR+CXCL Cytokines in Metastatic Kidney Cancers: Predictive Markers of Resistance to Sunitinib	• Metastatic Kidney Cancers	• Diagnostic Test: ELR+CXCL cytokines levels are of sunitinib response	• Centre Antoine LACASSAGNE Nice, France

Bispecific antibodies in cancer immunotherapy

Eva Dahlén, Niina Veitonmäki and Per Norlén



Therapeutic Advances in Vaccines and Immunotherapy

2018, Vol. 6(1) 3–17

DOI: 10.1177/
2515135518763280

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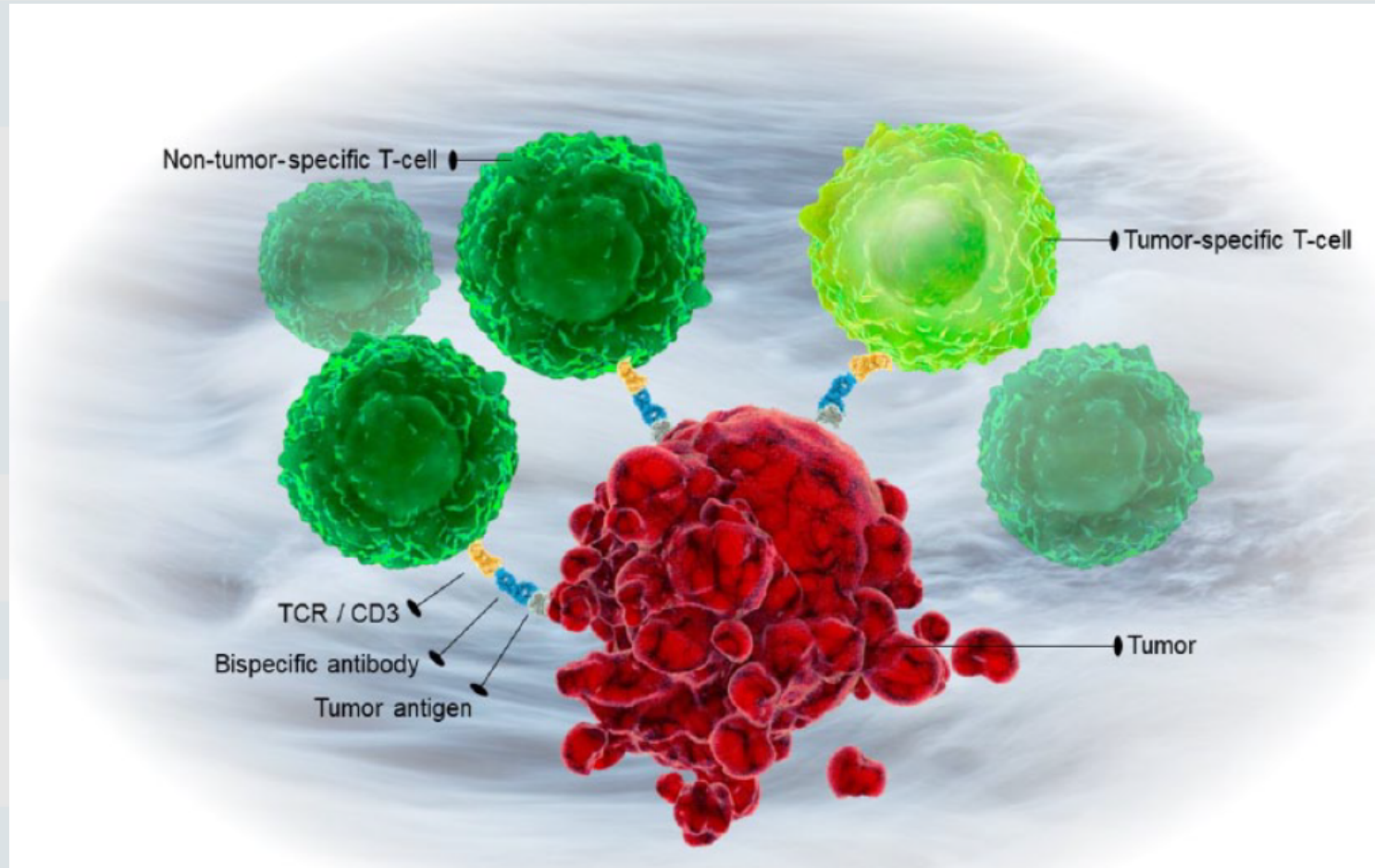
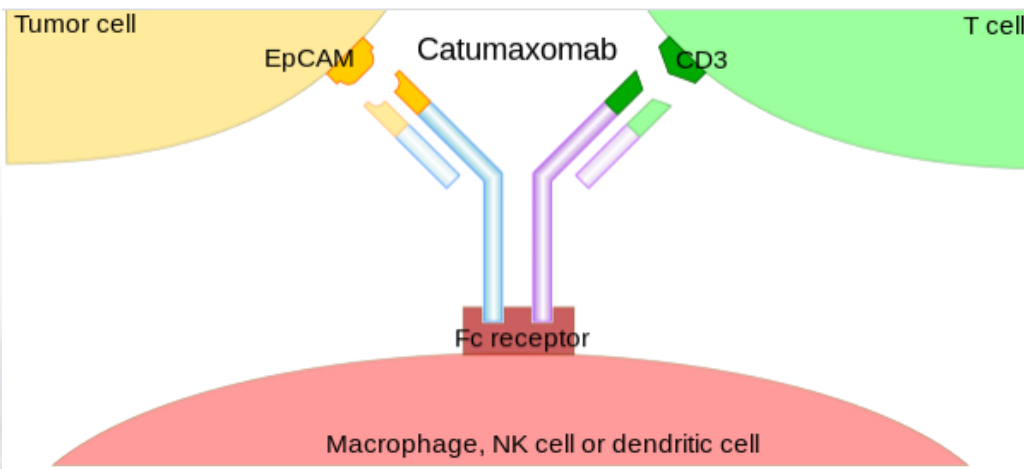
Class	Description	Targets	Examples	Stage*	Tumor-targeted immunomodulators	Directs potent costimulation to the tumor-infiltrating immune cells by targeting a tumor antigen and costimulatory molecules such as CD40 or 4-1BB	TA × CD40	ABBV-428	I
T-cell redirectors	Redirects T cells to malignant cells by targeting a tumor antigen and CD3	CD19 × CD3	Blinatumomab	Market					
		EpCAM × CD3	Catumaxomab	Marketed (withdrawn)			HER2 × 4-1BB	PRS343	I
		CD20 × CD3	XmAb13676 BTCT4465A R07082859	I			FAP × 4-1BB	4-1BB agonist	PC
		CD123 × CD3	MGD006 JNJ-63709178 Xmab14045	I	Dual immunomodulators	Simultaneous targeting of two immunomodulating targets, resulting in blockade of inhibitory targets, depletion of suppressive cells or activation of effector cells	5T4 × 4-1BB	ALG.APV-527	PC
		BCMA × CD3	JNJ-64007957 BI 836909	I			PD-L1 × TGF-β	M7824	I
		B7H3 × CD3	MGD009	I			PD-1 × LAG-3	MGD013	I
		CEA × CD3	R06958688 MT111	I				FS118	PC
		PSMA × CD3	Pasotuximab ES414/MOR209	I			PD-1 × TIM-3	MCLA-134	PC
NK-cell redirectors	Redirects NK cells to malignant cells by targeting a tumor antigen and CD16A	CD30 × CD16A	AFM13	II			PD-1 × CTLA-4	XmAb20717	PC
		EGFR × CD16A	AFM24	PC			CTLA-4 × OX40	ATOR-1015	PC
		BCMA × CD16A	AFM26	PC					

Classes Of Bispecific Antibodies In Cancer Immunotherapy

Based on the types of biological targets and modes of action, bispecific immunotherapies can be divided into three main categories:

- (1) Cytotoxic effector cell redirectors, including
 - (a) T-cell redirectors
 - (b) NK-cell redirectors
- (2) Tumor-targeted immunomodulators
- (3) Dual immunomodulators.

Cytotoxic Effector Cell Redirectors

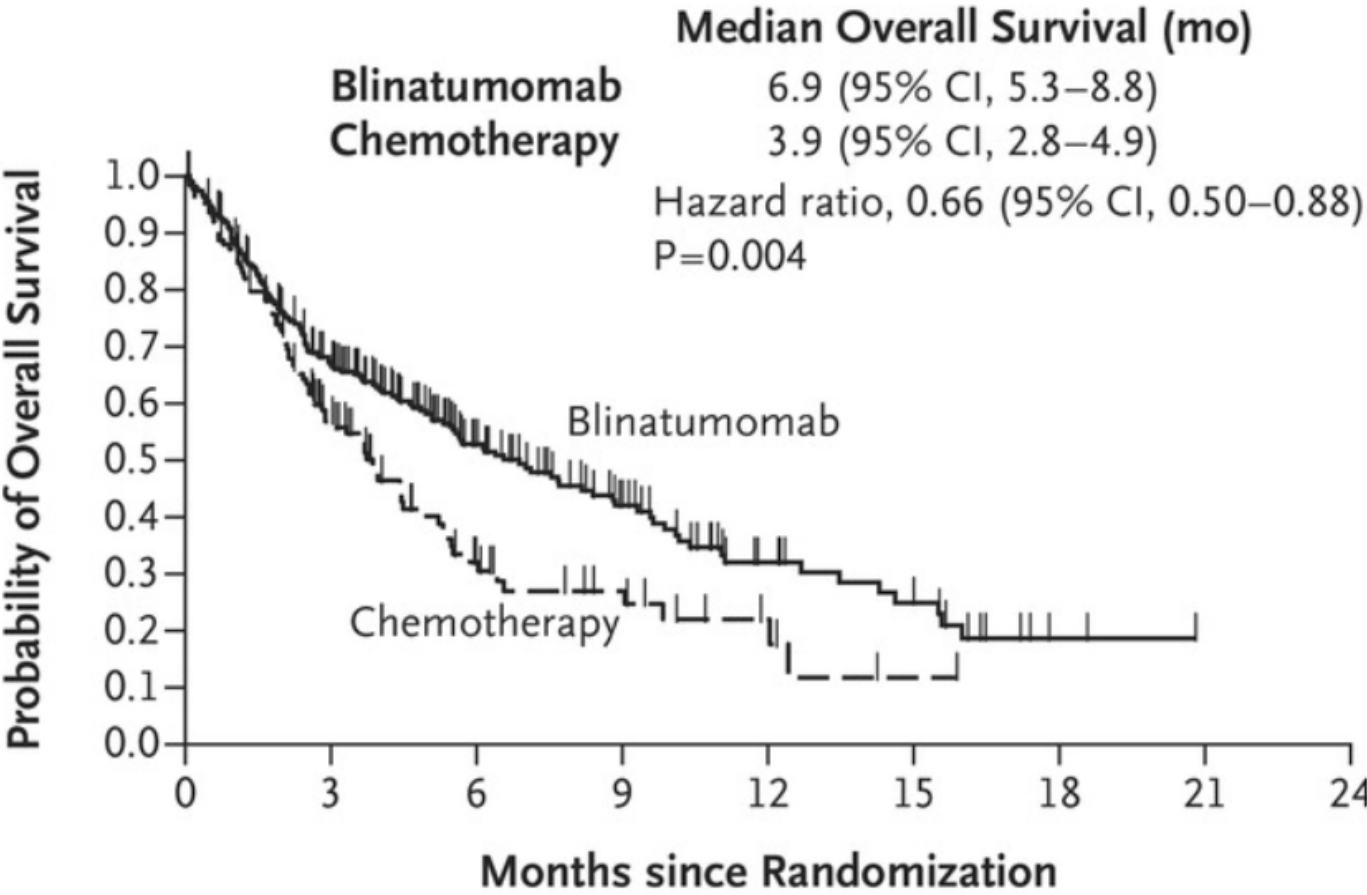
Class	Description	Targets	Examples	Stage*
T-cell redirectors	Redirects T cells to malignant cells by targeting a tumor antigen and CD3	CD19 × CD3	Blinatumomab	Market
		EpCAM × CD3	Catumaxomab	Marketed (withdrawn)
				
		B7H3 × CD3	MGD009	I
		CEA × CD3	R06958688 MT111	I
		PSMA × CD3	Pasotuximab ES414/MOR209	I

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

[March 2, 2017](#) N Engl J Med 2017; 376:836-847

DOI: 10.1056/NEJMoa1609783 [Chinese 中文翻译](#)

Overall Survival Censored at Time of Stem-Cell Transplantation



No. at Risk

Blinatumomab	271	163	80	44	21	13	2	0	0
Chemotherapy	134	56	21	12	5	1	0	0	0

Cytotoxic Effector Cell Redirectors-NK

Class	Description	Targets	Examples	Stage*
CD4 ⁺ T cells	T _H 1 T-bet IFN- γ	CD30 $\times$ CD16A	AFM13	II
	T _H 2 GATA-3 IL-4 IL-5 IL-13	EGFR $\times$ CD16A	AFM24	PC
	T _H 17 and T _H 22 ROR γ t IL-17 IL-22	BCMA $\times$ CD16A	AFM26	PC
B cells	CLP			
Killer T cells	CD8 ⁺ Eomes IFN- γ			
	NK			
Helper-like ILCs	ILC1 T-bet			
	ILC2 GATA-3			
	ILC3 ROR γ t NKp46 ⁺ ROR γ t NKp46 ⁻			
Killer ILCs				

Diagram illustrating the differentiation of Cytotoxic Effector Cells (CECs) from a Common Lymphoid Precursor (CLP) and the application of Cytotoxic Effector Cell Redirectors (CERs) in cancer therapy.

CLP Differentiation:

- CD4⁺ T cells:** T_H1 (T-bet, IFN- γ), T_H2 (GATA-3, IL-4, IL-5, IL-13), T_H17 and T_H22 (ROR γ t, IL-17, IL-22).
- Helper-like ILCs:** ILC1 (T-bet), ILC2 (GATA-3), ILC3 (ROR γ t, NKp46⁺, ROR γ t, NKp46⁻).
- B cells:** CLP.
- Killer T cells:** CD8⁺ (Eomes, IFN- γ), NK (Eomes).

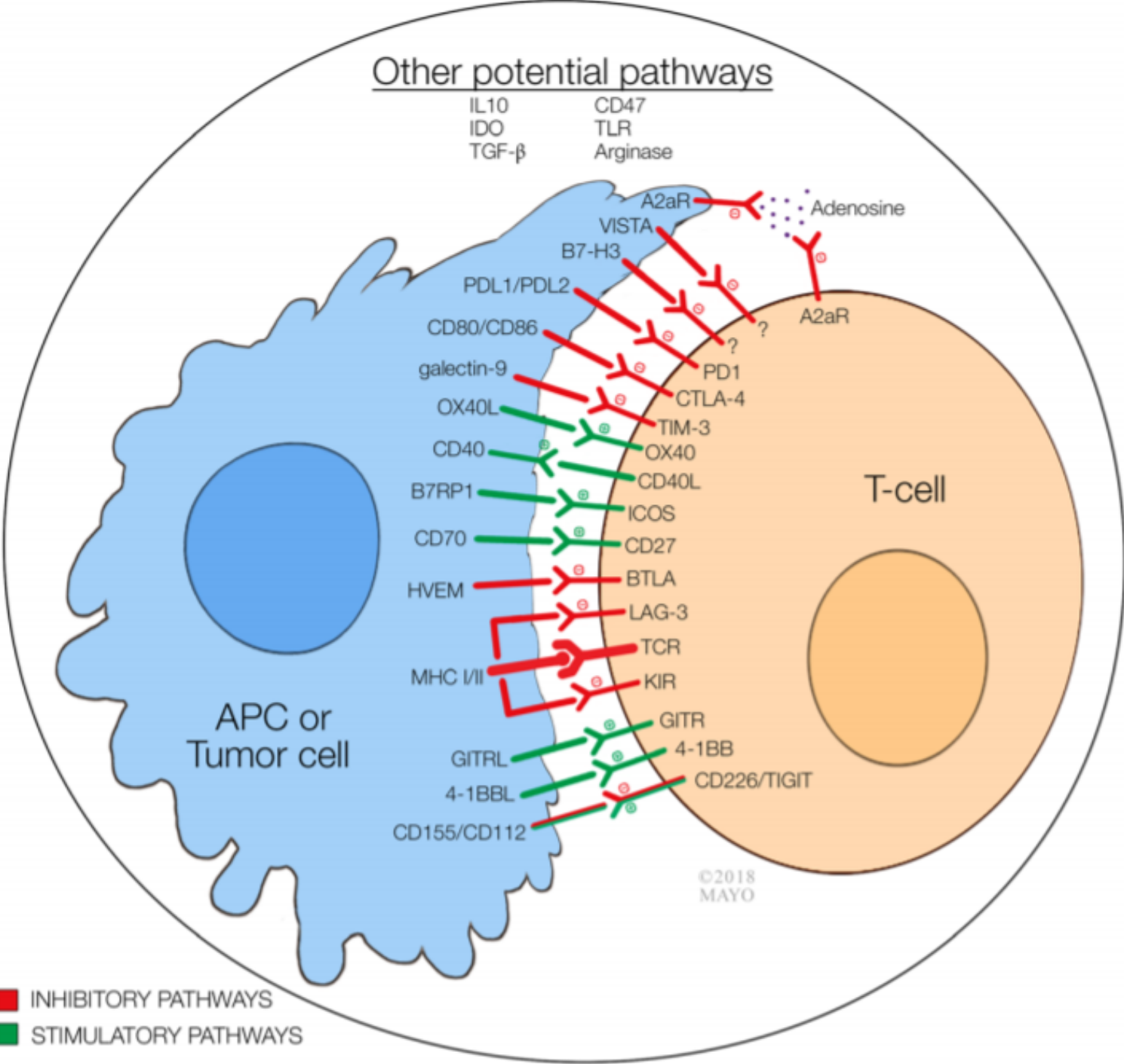
Cytotoxic Effector Cell Redirectors (CERs) Examples:

Class	Description	Targets	Examples	Stage*
CD4 ⁺ T cells	T _H 1	CD30 $\times$ CD16A	AFM13	II
CD4 ⁺ T cells	T _H 2	EGFR $\times$ CD16A	AFM24	PC
CD4 ⁺ T cells	T _H 17 and T _H 22	BCMA $\times$ CD16A	AFM26	PC

Diagram illustrating the mechanism of Cytotoxic Effector Cell Redirectors (CERs):

- Non-tumor-specific T-cell
- Tumor-specific T-cell
- TCR / CD3
- Bispecific antibody
- Tumor antigen
- Tumor

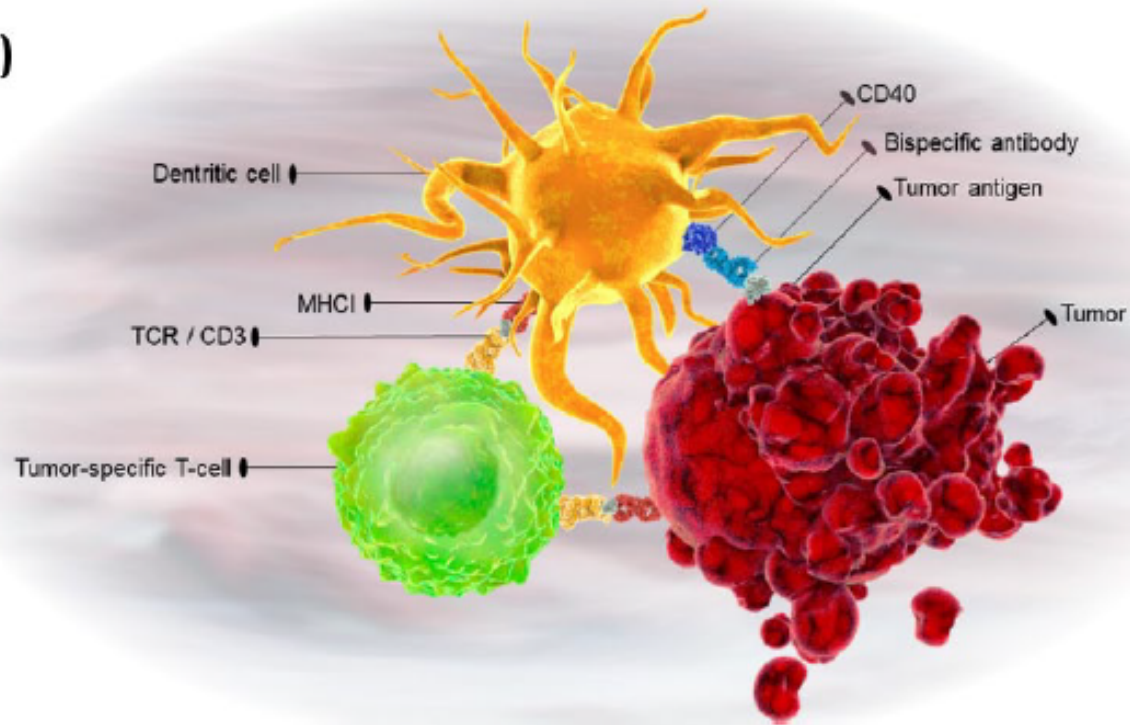
Class
Tumor-targeted immunomodulators
Dual immunomodulators



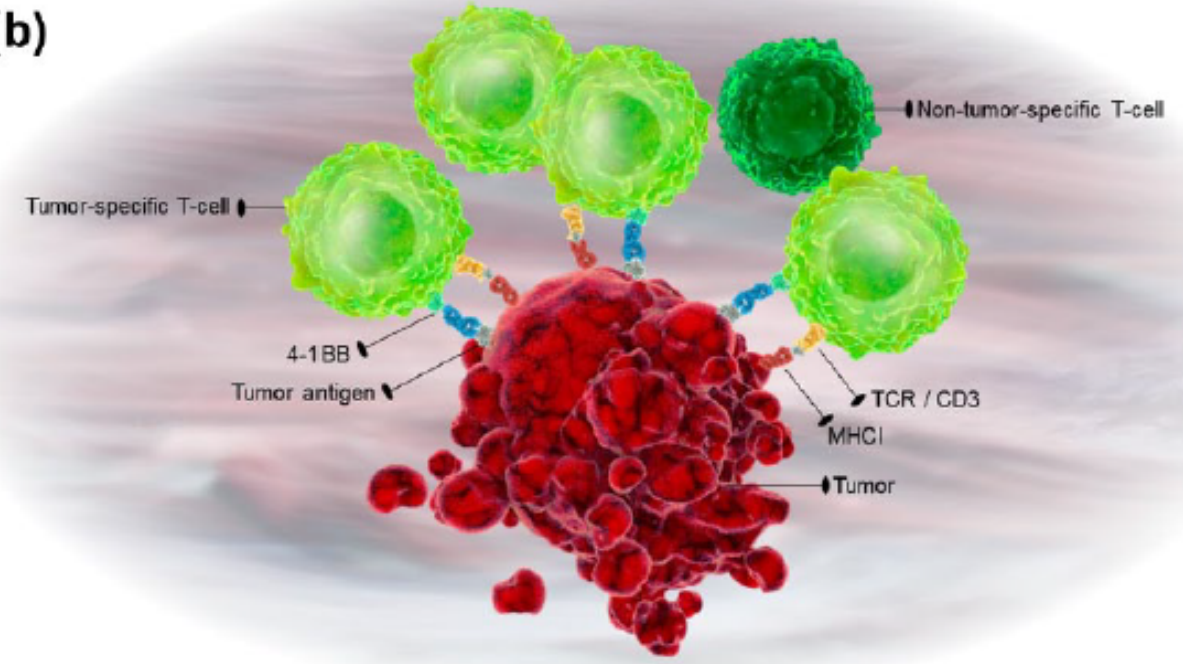
es	Stage*
428	I
3	I
agonist	PC
2V-527	PC
	I
13	I
	PC
134	PC
20717	PC
1015	PC

Tumor Targeted Immunomodulators

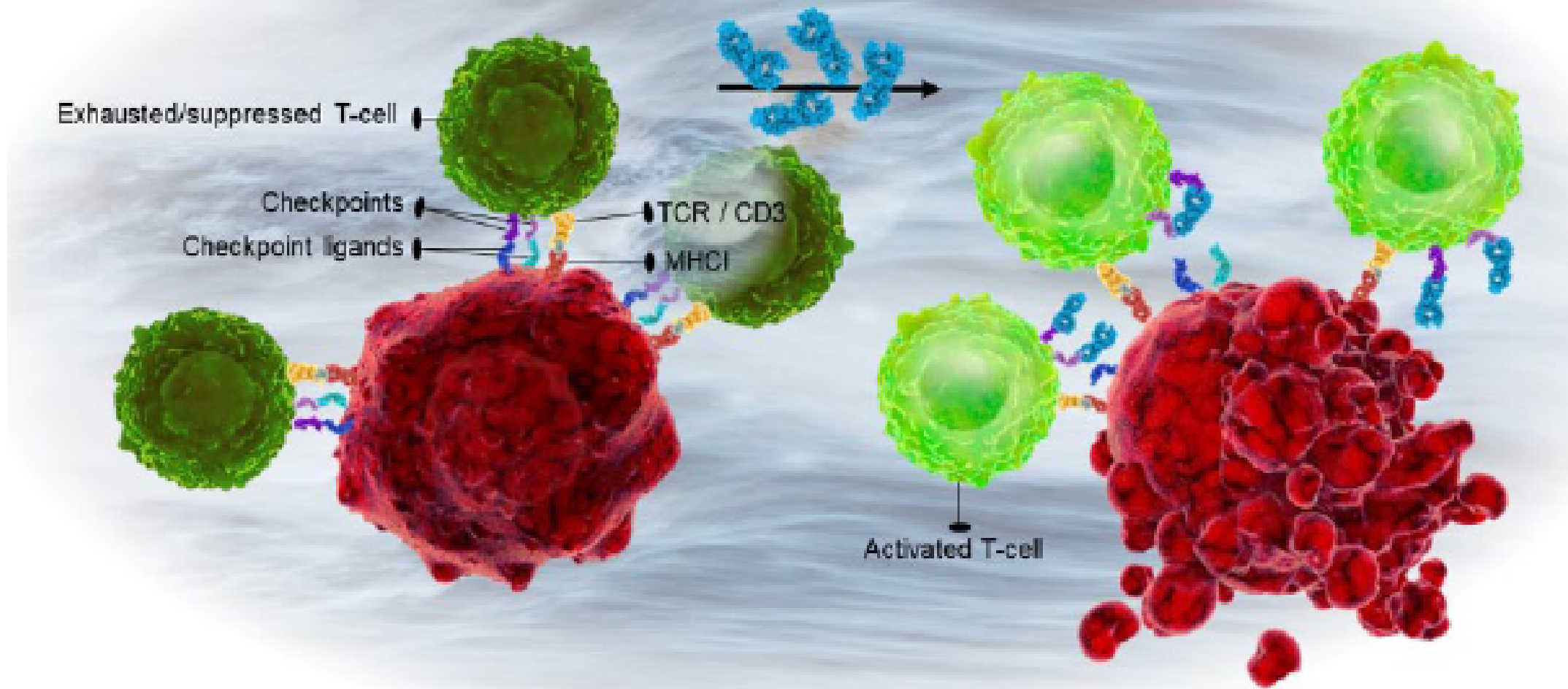
(a)

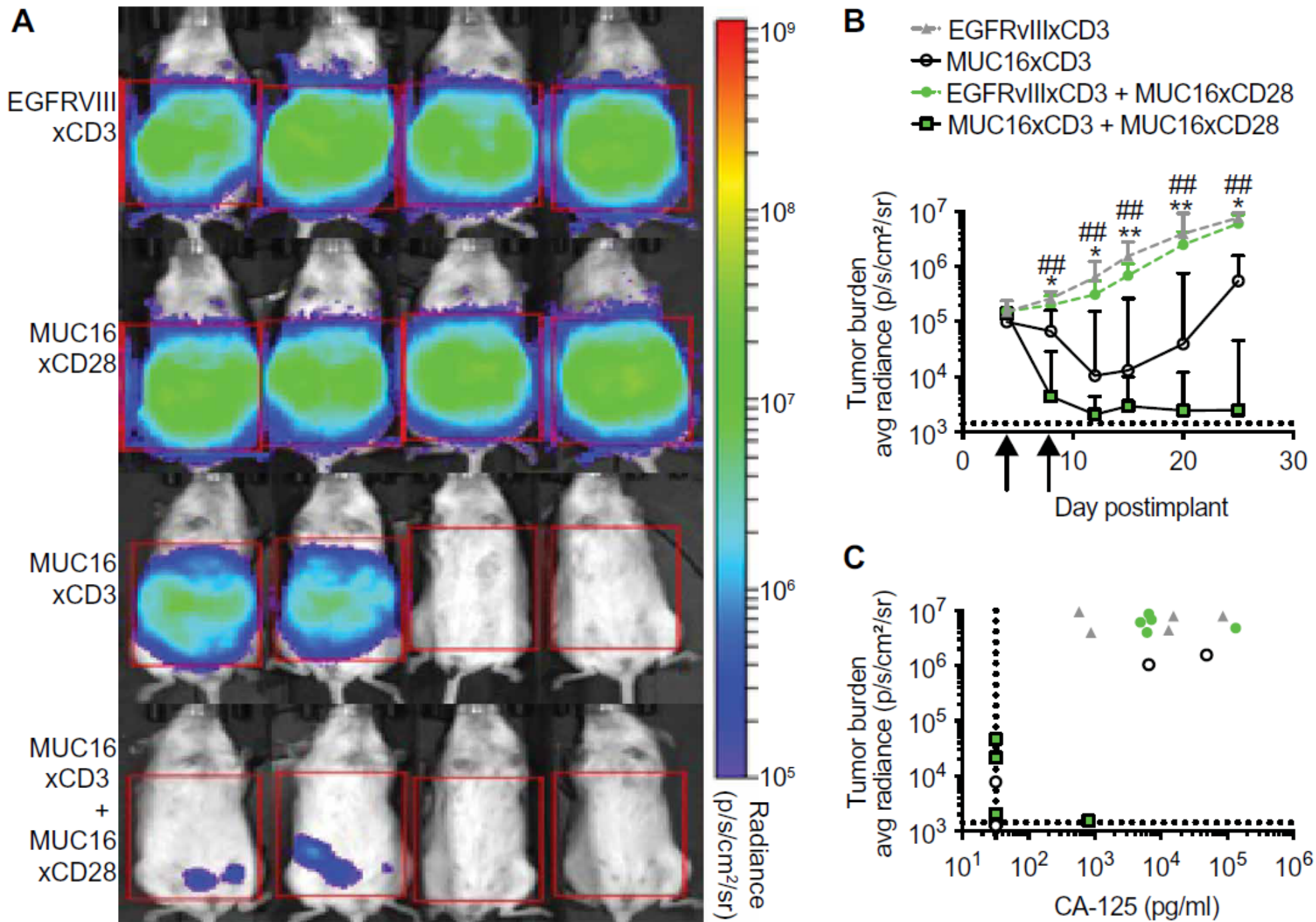
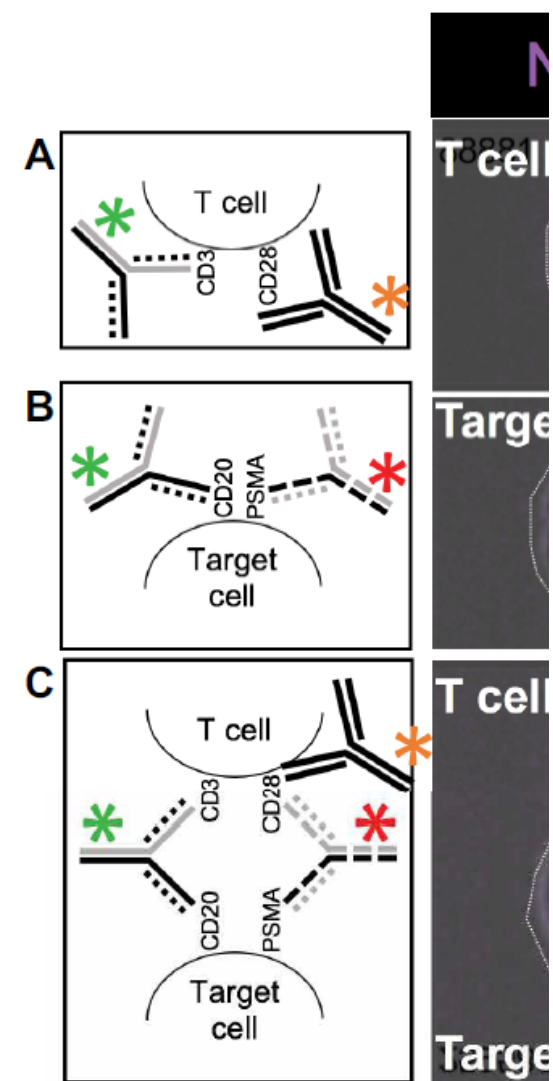


(b)



Dual Tumor Targeted Immunomodulators





CD40 Agonists Alter Tumor Stroma and Show Efficacy Against Pancreatic Carcinoma in Mice and Humans

Gregory L. Beatty, *et al.*

Science **331**, 1612 (2011);

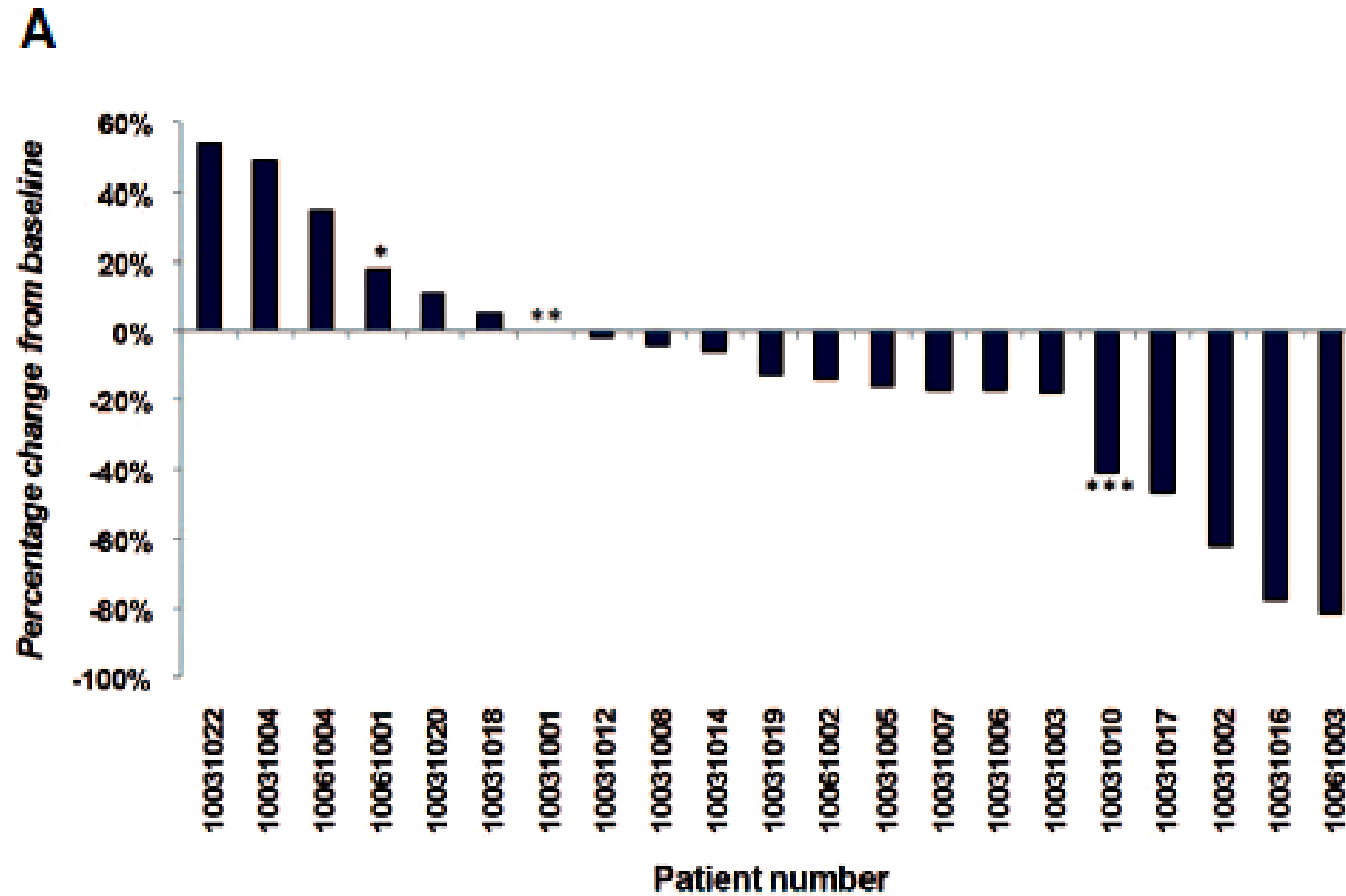
DOI: 10.1126/science.1198443

Gregory L. Beatty,^{1,2,6} Elena G. Chiorean,³ Matthew P. Fishman,¹ Babak Saboury,⁵
Ursina R. Teitelbaum,^{2,6} Weijing Sun,^{2,6} Richard D. Huhn,⁴ Wenru Song,⁴ Dongguang Li,⁴
Leslie L. Sharp,⁴ Drew A. Torigian,^{2,5} Peter J. O'Dwyer,^{2,6} Robert H. Vonderheide^{1,2,6*}

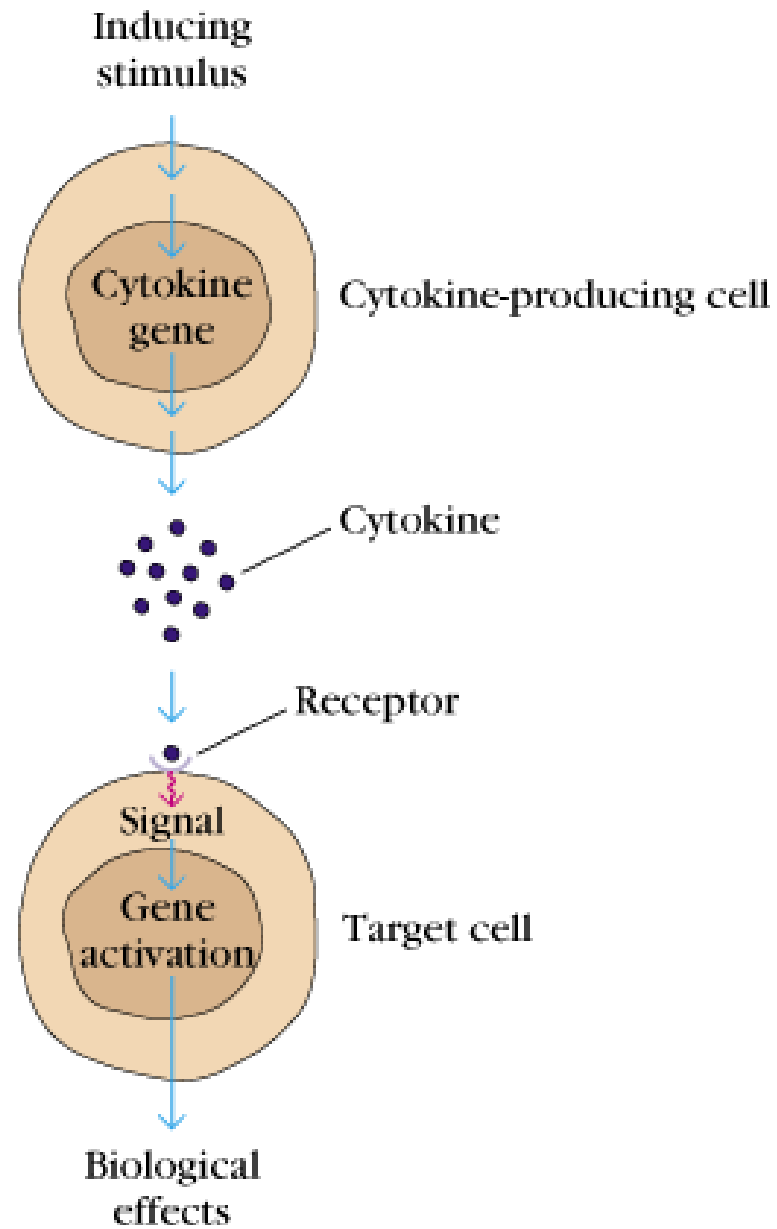
¹Abramson Family Cancer Research Institute, University of Pennsylvania School of Medicine, 421 Curie Boulevard, Philadelphia, PA 19104, USA. ²Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. ³Division of Hematology/Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202, USA. ⁴Pfizer Corporation, New London, CT 06320, USA. ⁵Department of Radiology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. ⁶Division of Hematology-Oncology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA.

*To whom correspondence should be addressed. E-mail: rhv@exchange.upenn.edu

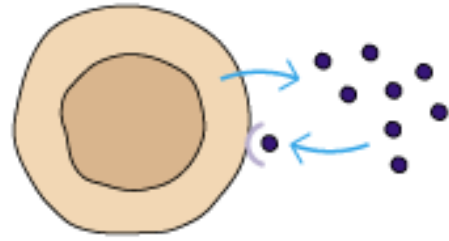
Fig. 1. Agonist CD40 mAb in combination with gemcitabine induces clinical responses in patients with surgically incurable PDA.



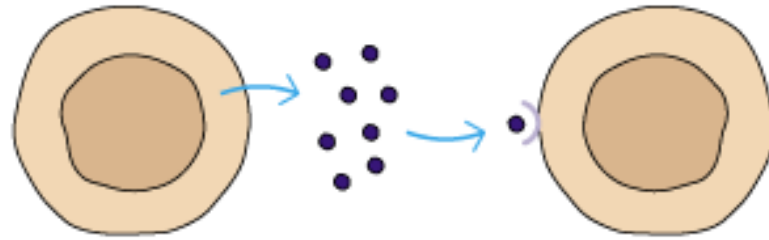
General properties of cytokines



General properties of cytokines

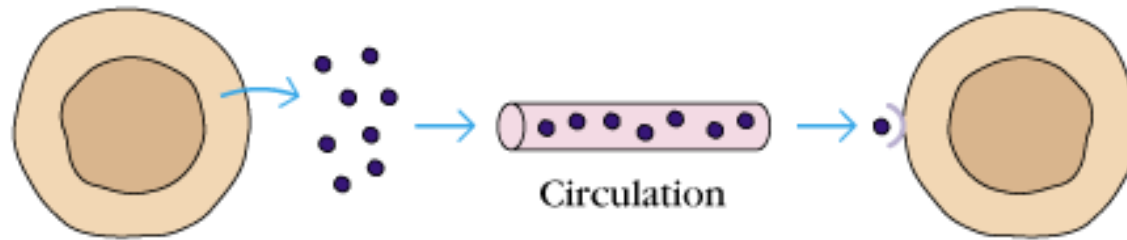


Autocrine action



Paracrine action

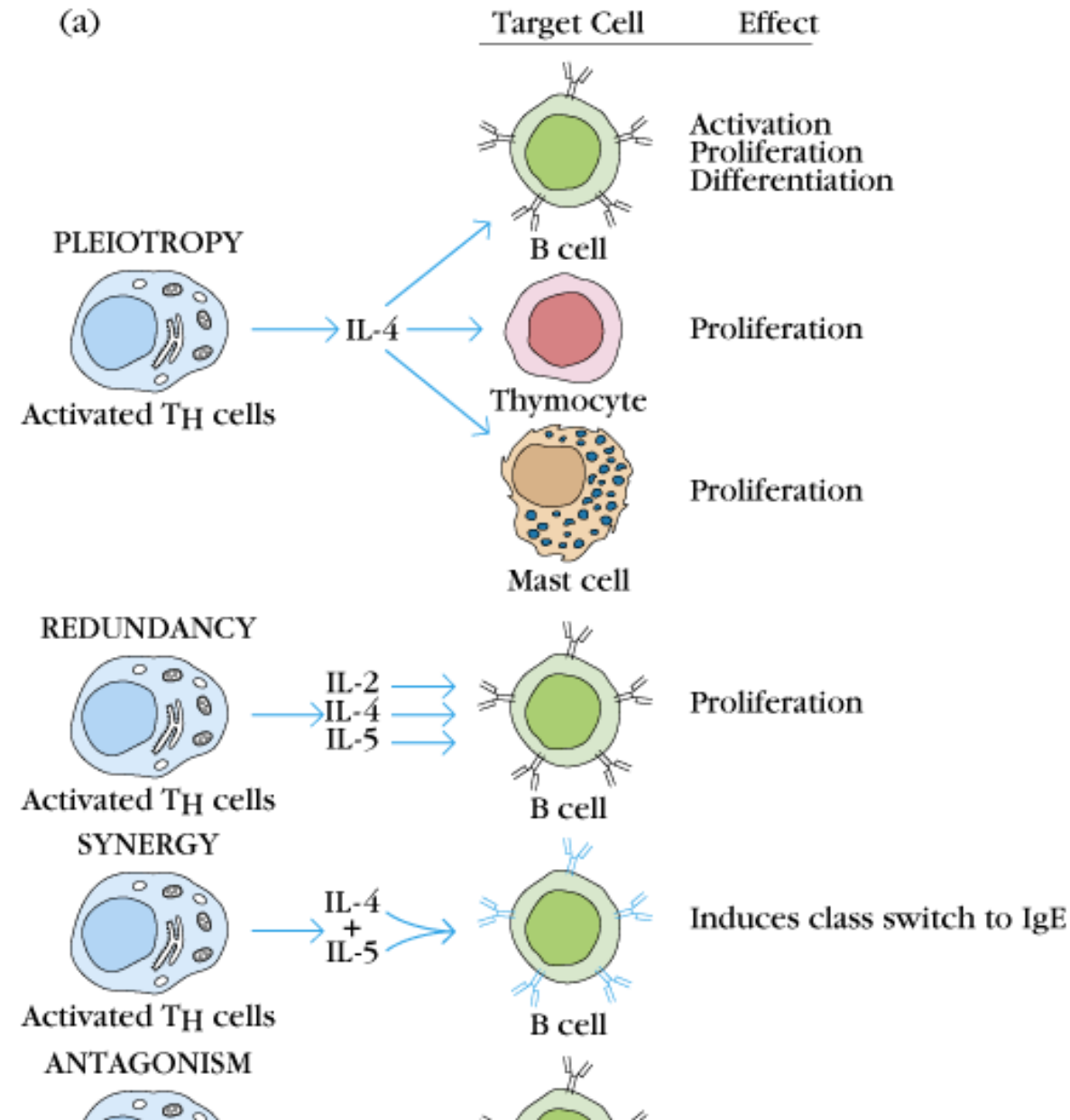
Nearby cell



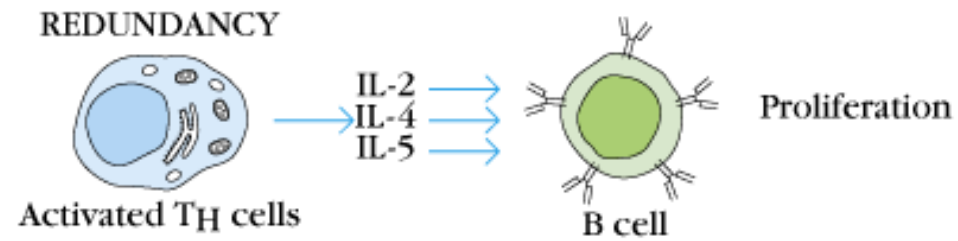
Endocrine action

Distant cell

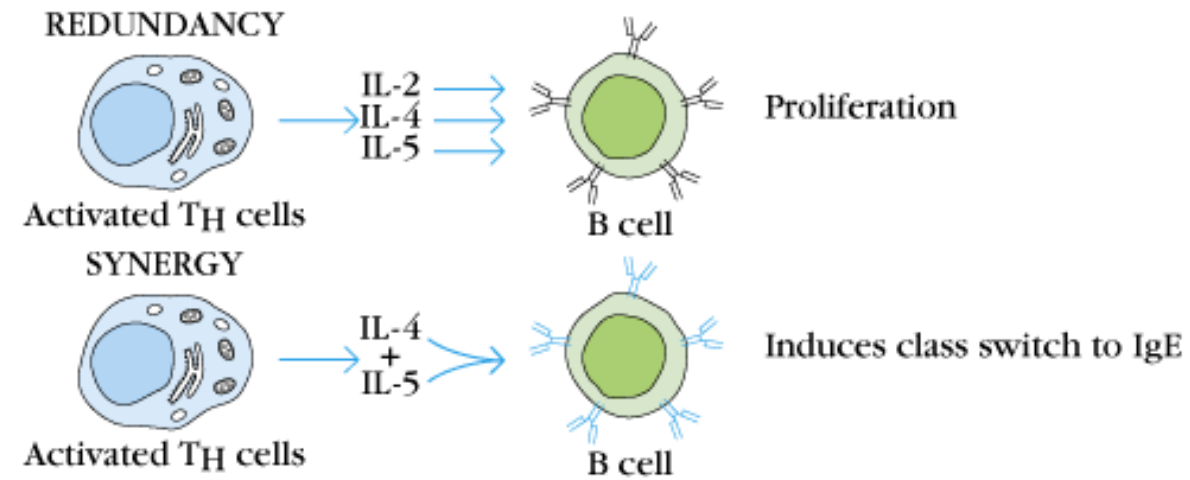
General Properties Of Cytokines



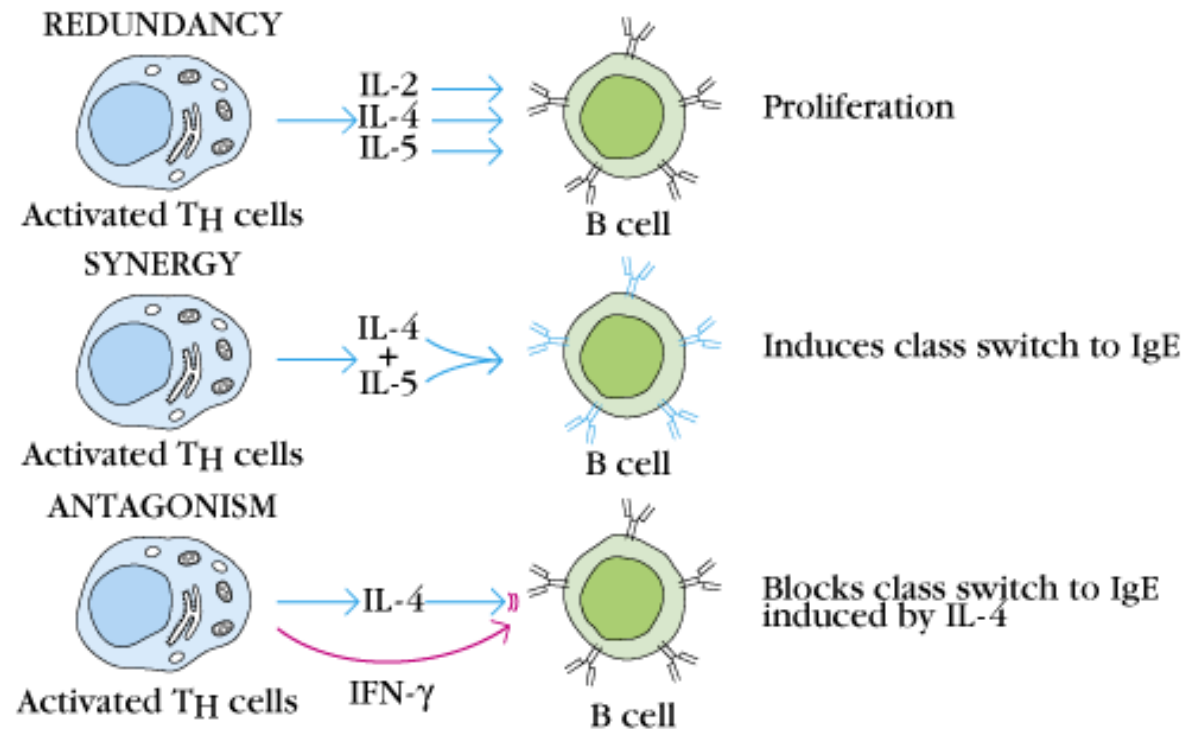
General Properties Of Cytokines



General properties of cytokines



General Properties Of Cytokines



Role of Cytokines in Promoting Cancer (Dranoff Review)

Cytokine	Cellular sources	Role in tumour formation
Il-1	Macrophages, dendritic cells, B cells, natural killer cells, keratinocytes	Required for tumour invasion and angiogenesis
Il-6	Macrophages, T cells, B cells, endothelial cells, fibroblasts	Required for chemically induced lymphoma
Il-12	Macrophages, dendritic cells, neutrophils	Inhibits chemical carcinogenesis
Il-15	Macrophages, dendritic cells	Promotes natural killer T cell leukaemias
Ifn- γ	Natural killer cells, natural killer T cells, T cells, B cells, macrophages, dendritic cells	Inhibits chemical carcinogenesis; inhibits lymphomas (especially with perforin); Stat1 and Rag2 inhibit carcinomas
M-csf	Macrophages, endothelial cells, fibroblasts, bone-marrow stroma	Promotes breast cancer invasion
Gm-csf	Respiratory epithelial cells, T cells, natural killer cells, natural killer T cells, macrophages, eosinophils, endothelial cells, fibroblasts	Inhibits lymphomas and carcinomas (with Ifn- γ and Il-3)
Tnf- α	Macrophages, natural killer cells, B cells, T cells, neutrophils, fibroblasts, keratinocytes	Required for chemically-induced skin cancer
Mif	Macrophages, T cells, eosinophils, fibroblasts, keratinocytes, pituitary	Inhibits p53 tumour-suppressor functions
Tgf- β	T cells, B cells, macrophages, platelets, bone-marrow stroma, eye, testis	Inhibits colon carcinomas (with Rag2)
Fas– Fas ligand	B cells, T cells, hepatocytes, colon, ovary, respiratory epithelial cells	Inhibits lymphomagenesis

Clinical Administration of Cytokines (Dranoff)

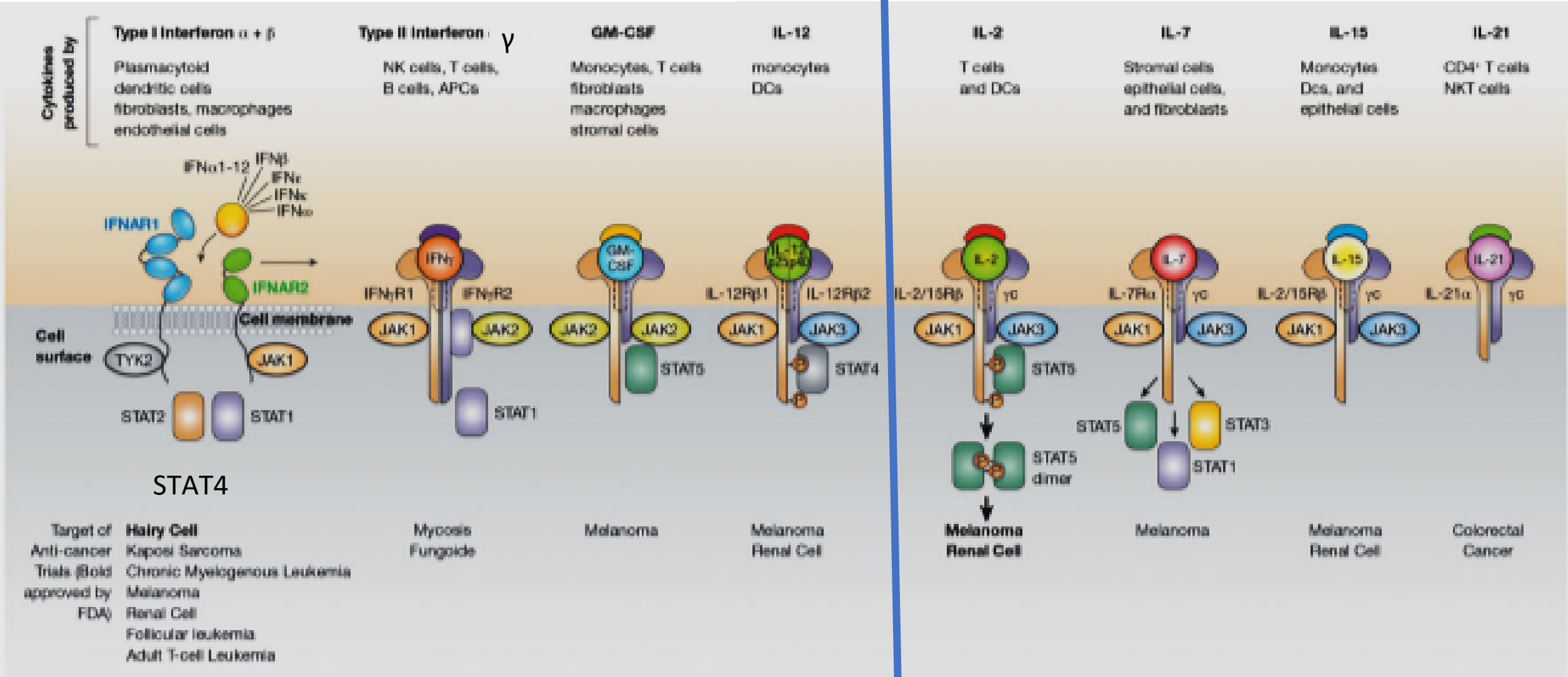
Cytokine	Therapeutic actions	Clinical administration
IL-2	Enhances NK cell and CD8 ⁺ T-cell function; increases vascular permeability	Systemic, local
IL-3	Enhances tumour antigen presentation	Systemic
IL-4	Enhances eosinophil function and T-cell activation	Systemic, local
IL-6	Enhances T-cell and B-cell function; inhibition of IL-6 reduces lymphoproliferation	Systemic, local
IL-7	Enhances T-cell function	Local
IL-10	Inhibits tumour antigen presentation	Pending
IL-12	Enhances T _H 1 immunity and cytotoxicity; inhibits angiogenesis	Systemic, local
IL-13	Inhibits cytotoxicity against viral neoplasms	Pending
IL-15	Enhances cytotoxicity	Pending
IL-18	Enhances T _H 1 immunity and cytotoxicity; inhibits angiogenesis	Pending
M-CSF	Enhances macrophage function	Systemic
GM-CSF	Enhances tumour antigen presentation	Systemic, local
IFN- α	Enhances tumour antigen presentation and cytotoxicity	Systemic
IFN- γ	Enhances tumour antigen presentation and cytotoxicity	Systemic, local
TNF- α	Induces tumour-cell apoptosis; activates endothelium and granulocytes	Systemic
TRAIL	Induces tumour-cell apoptosis	Pending
FLT3 ligand	Stimulates dendritic-cell and NK-cell function	Systemic
Lymphotoctin	Enhances T-cell recruitment	Local
TGF- β	Inhibits T-cell effector function	Pending

Cytokines in the Treatment of Cancer

Kevin C. Conlon, Milos D. Miljkovic, and Thomas A. Waldmann

IL23
IL27
IL35

And IL-4 and IL-9 (mast cells)



Cytokines are medically relevant endogenous small (~15kDa) proteins

Cytokine-based therapies in human disease

Cytokine	Brand name	Status	Indication	Year of 1 st FDA Approval
IL-2	Proleukin	Approved	Cancer	1992
IL-11	Neumega	Approved	Thrombocytopenia	1994
EPO	Epogen	Approved	Anemia	1989
G-CSF	Neupogen	Approved	Myelosuppression from chemo	1991
GM-CSF	Leukine	Approved	Myelosuppression from chemo	1991
IFN- α	Intron-A	Approved	Hepatitis, Cancer	1991
IFN- β	Betaseron	Approved	Multiple sclerosis	1993
IFN- γ	Actimmune	Approved	Granulomatosis	1990
IL-7		Clin dev	Cancer, anti-viral	
IL-10		Clin Dev	Cancer, anti-inflammatory	
IL-12		Clin dev	Cancer, anti-viral	
IL-15		Clin dev	Cancer	
IL-21		Clin dev	Cancer	

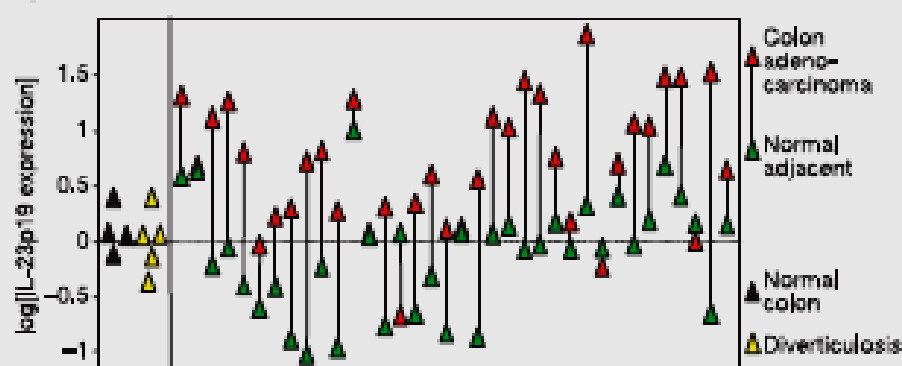
IL23

May 2006

LETTERS

IL-23 promotes tumour incidence and growth

John L. Langowski^{1*}, Xueqing Zhang^{1*}, Lingling Wu¹, Jeanine D. Mattson¹, Taiying Chen¹, Kathy Smith¹, Beth Basham¹, Terrill McClanahan¹, Robert A. Kastelein¹ & Martin Off¹



b

Cancer type	Number of paired (tumour and normal) samples	Fold increase in expression		p
		Average	Number >5x Number >10x	
Colon	38	15.33	23 17	0.0001
Ovarian	32	9.45	12 4	0.0001
Head and neck	44	3.41	11 4	0.01
Lung	114	3.03	20 8	0.0001
Breast	78	2.86	16 6	0.0001
Stomach	64	2.13	9 3	0.001
Melanoma	89	1.47	5 0	0.0001

c

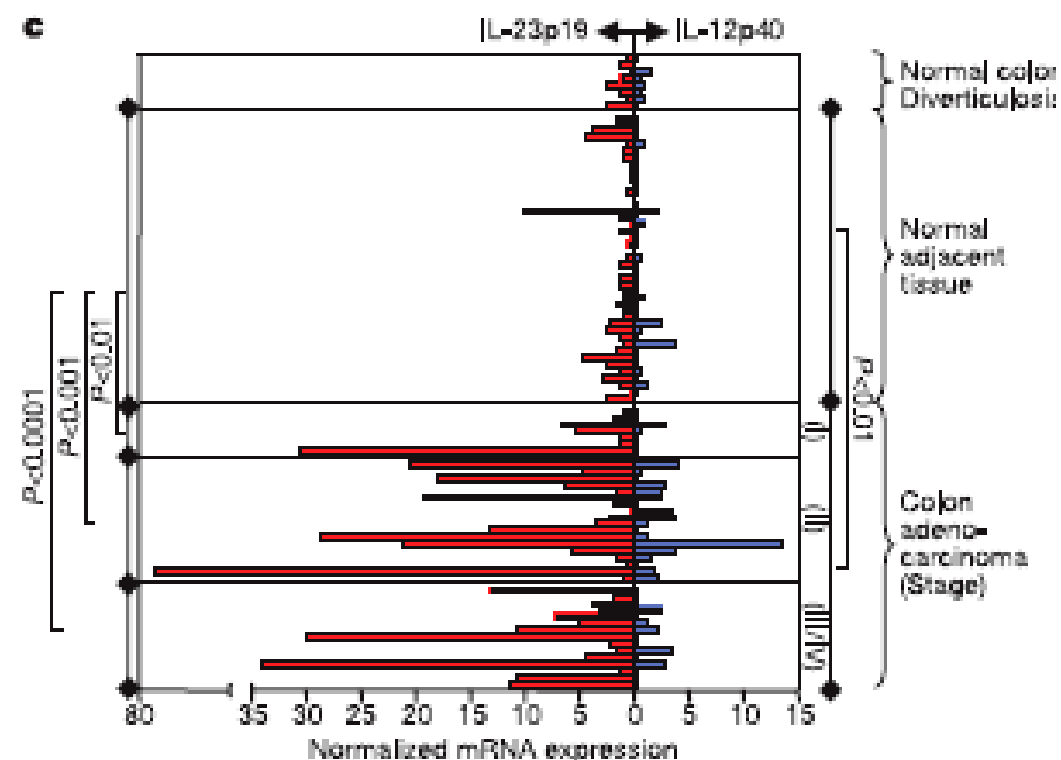


Figure 1 | Overexpression of IL-23 but not of IL-12 in human cancer.

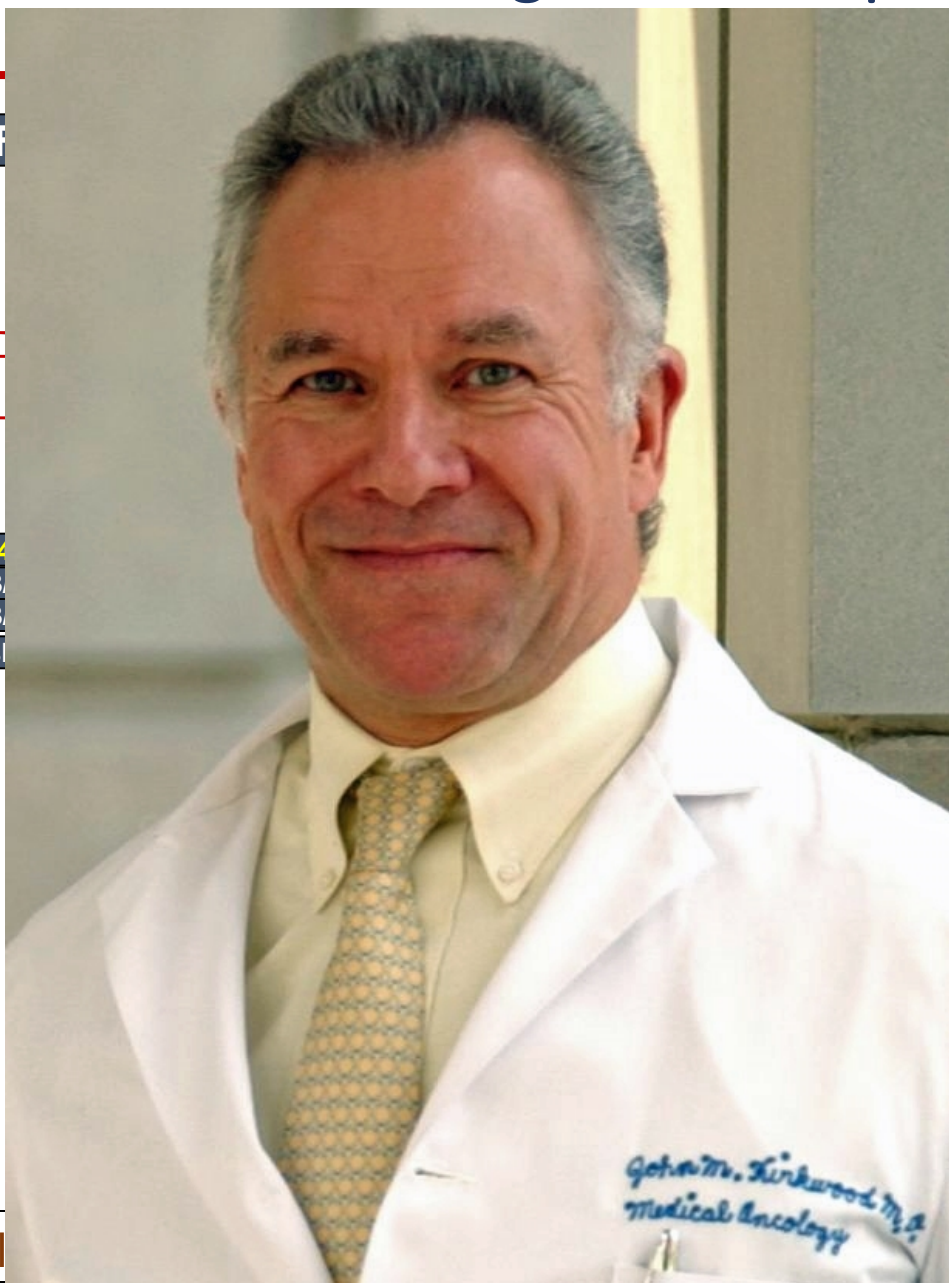
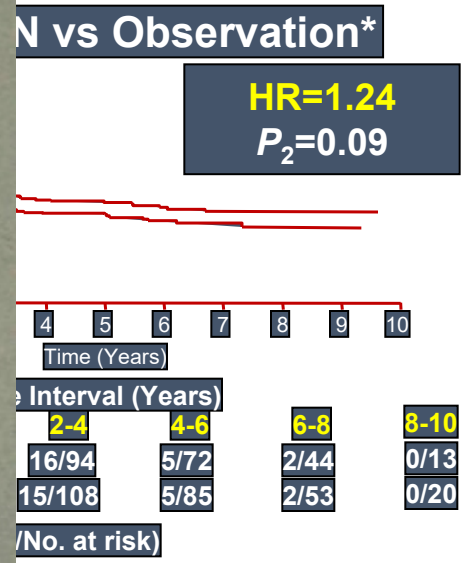
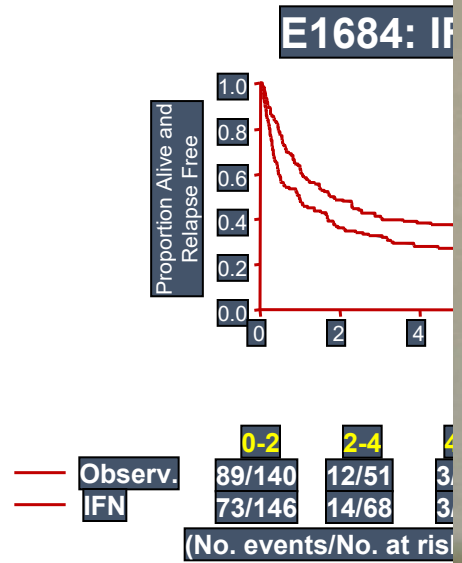
The Beginning of Molecular Therapeutics - 1978

PEOPLE.COM • ARCHIVE

Will Interferon Kill Cancer? Finnish Dr. Kari Cantell Is Helping the World Find Out

But Cantell and the Finnish Red Cross, now producing 250 billion units (5,285 quarts) a year, have provided the great bulk of pure interferon used for clinical studies on humans, including a \$2 million batch bought last year by the American Cancer Society. "Production is the bottleneck," says Cantell, who finds it "stupid and irritating" that until recently nobody else has tried to produce the substance in large-scale volume.

E1684, E1690, and E1694: Durable and significant Impact upon relapse-free * and



Meta-analysis impact

Kirkwood. *Clin Cancer Res.* 2004;10:1670; Wheatley, Ives et al., 2007, 2008

Interferon Alpha

- IFNa and Peginterferon alpha 2b are approved as adjuvant treatment for patients with completely resected stage III or IV high-risk melanoma
- Adjuvant in Melanoma (Kirkwood/ECOG); On February 15, 2019, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck) for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- First-line treatment for patients with mRCC (alfa-2a, and alfa-2b in combination with bevacizumab),
- AIDS-related Kaposi's sarcoma (alfa-2b), follicular lymphoma (alfa-2b), HCL (alfa-2a, alfa-2b), chronic myelogenous leukemia (Philadelphia chromosome-positive alfa-2a),
- Condyloma acuminata (alfa-2b), and cervical intraperitoneal neoplasms (alfa-2b) (Guttermann and others 1980; Kirkwood and Ernstoff 1984; Windbichler and others 2000).
- Pegylated for Hepatitis
- Hairy cell leukemia (BRAF mutant; purine analogues)

Interferon-gamma (IFN- γ)

- Only type II IFN
- Produced mainly by NK cells and T lymphocytes
- Works primarily as an immunomodulator
 - 100-10K x more active than Type I interferons
- Functions
 - Regulate MHC expression
 - Activates differentiation and function of phagocytes
 - Augments interactions between macrophages and T-cells
 - Key role in regulating T-cell subsets to determine the type of immune effector function during a specific immune response

INTERFERON GAMMA-1b
 MARTIN E. GLEAVE, /
 MALCOLM J. Mc

LAURENCE H. KLOTZ,
 ...GY GROUP

Final results of the EORTC 18871/DKG 80-1 randomised phase III
 trial: rIFN- α 2b versus rIFN- γ versus ISCADOR[®] versus
 observation after surgery in melanoma patients
 primary (thickness >3 mm) ...

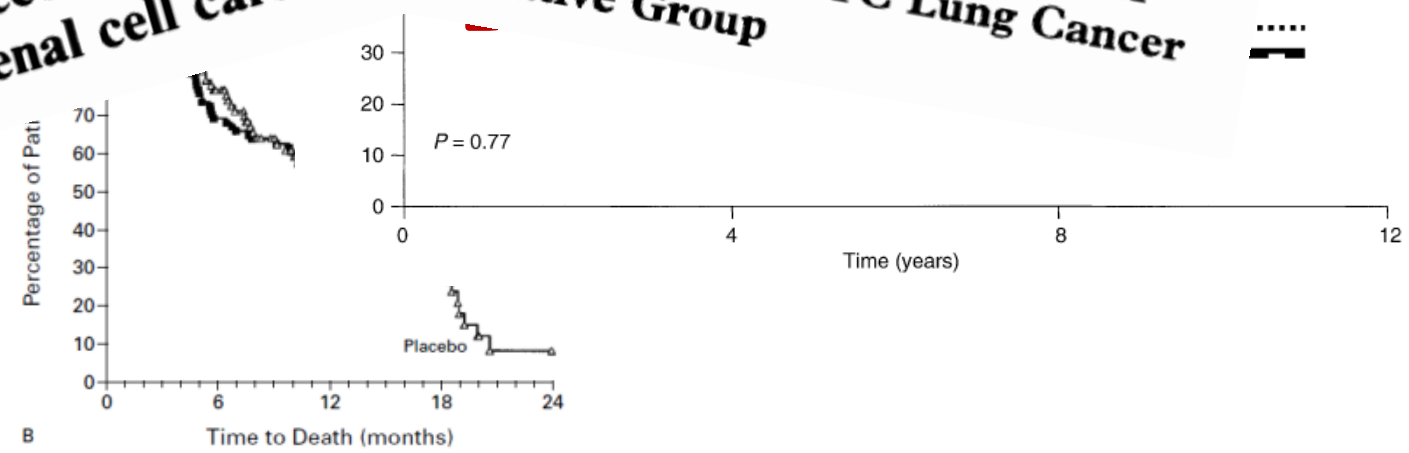
interferon
 with

FAILED!!!!!!

Role of Recombinant Interferon
 Response

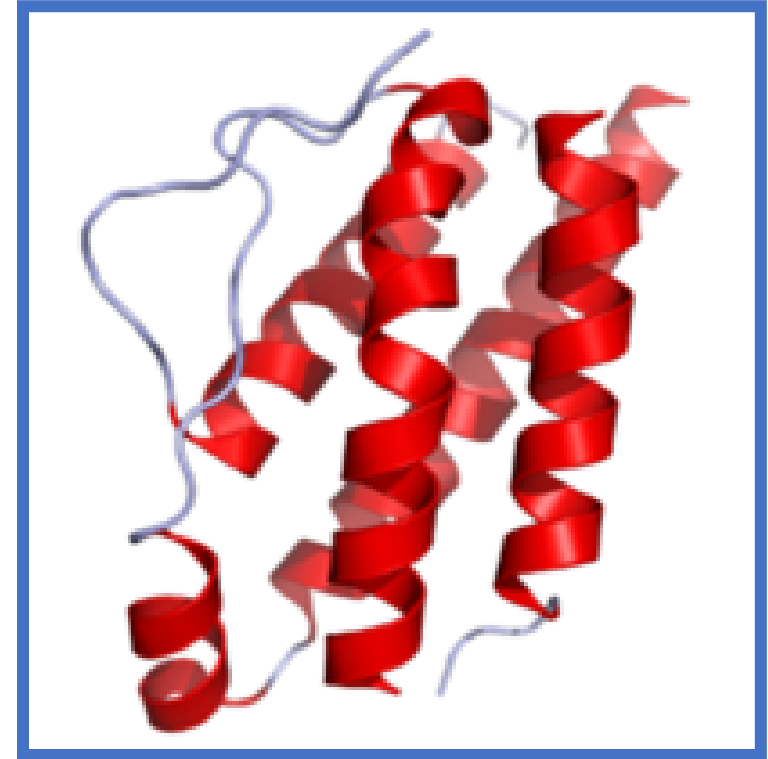
Phase Randomised phase III study
 EORTC (30885) randomised phase III study
 alpha and recombinant interferon alpha and gamma in pa
 advanced renal cell carcinoma

Maintenance in
 Cell Lung Cancer. A
 the EORTC Lung Cancer
 Active Group



Cytokines IFN α , IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-15, IL-18, IL-21, IL-24....IL-41

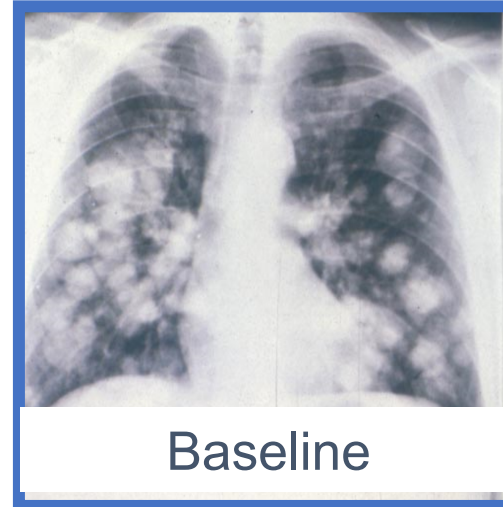
- IL-2 Discovered in 1976 and described as a protein that stimulated growth of T cells¹
- Jurkat IL-2 in 1983 [Lotze]
- Recombinant IL-2 first cloned in 1983¹
- First phase I studies of rIL-2 in malignant disease in 1984²
- Phase II clinical trials began in 1985³



1. Atkins MB, Lotze MT et al. *J Clin Oncol*. 1999;17;2105-2116.
2. Lotze MT et al *J Immunol*. 1985;134:157-166
3. Atkins MB et al. *J Clin Oncol*. 1986;4:1380-1391

High Dose IL-2 Immunotherapy

- Approved in patients with melanoma and kidney cancer.
- Significant 'toxicity'.
- Associated with 'cytokine storm'.
- iNOS blockers, sTNF-R or IL-1Ra have yielded limited reduction in side effects.
- IL-2 treatment is associated with a 'systemic autophagic syndrome' and temporally limited tissue dysfunction.



*AR. Chavez, X Liang, MT Lotze.
Ann. N.Y.Acad.Sci.1182:14-27 (2009)*

Return of
Jonah
John
Wehrle
1980



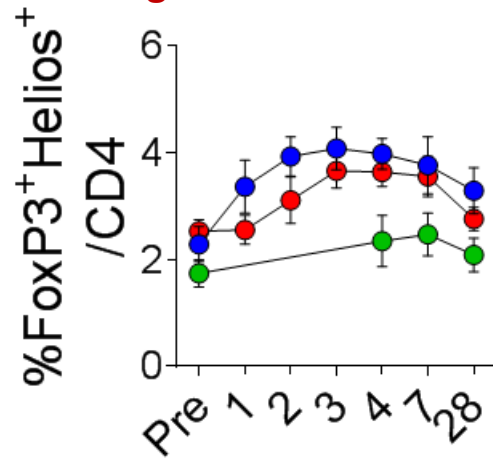
Dupont 1983
Taniguchi, N
Roche 9/84
Cetus-PEG
Chiron
Novartis
Prometheus
Nestle
Clinigen



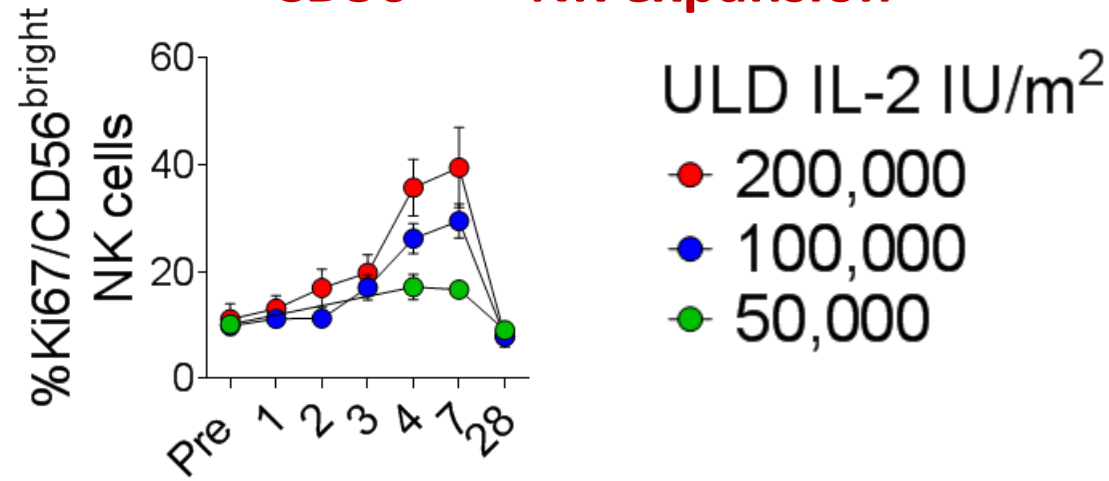
Paging Dr. Crick
John Wehrle

Ultra-low dose IL-2 expands regulatory T cells and NK cells in healthy donors

T_{regs} expansion



CD56^{bright} NK expansion



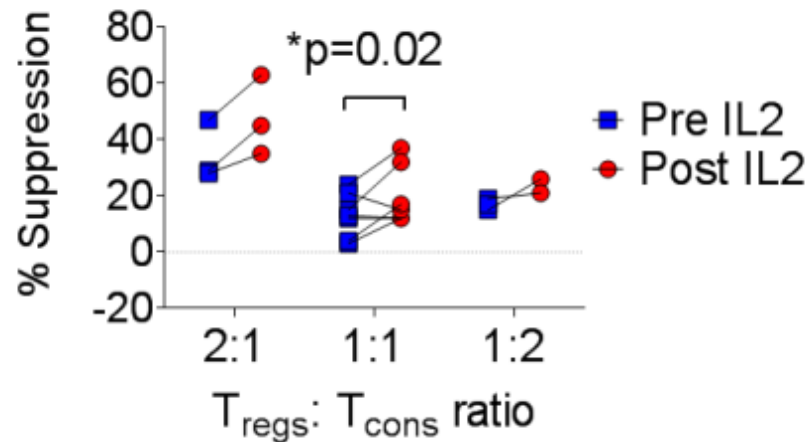
ULD IL-2 IU/m²

● 200,000

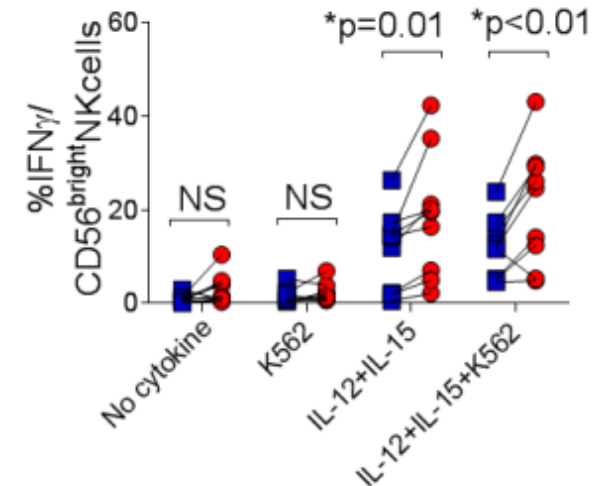
● 100,000

● 50,000

Increased T_{reg} suppression



Enhanced IFN γ production in NK

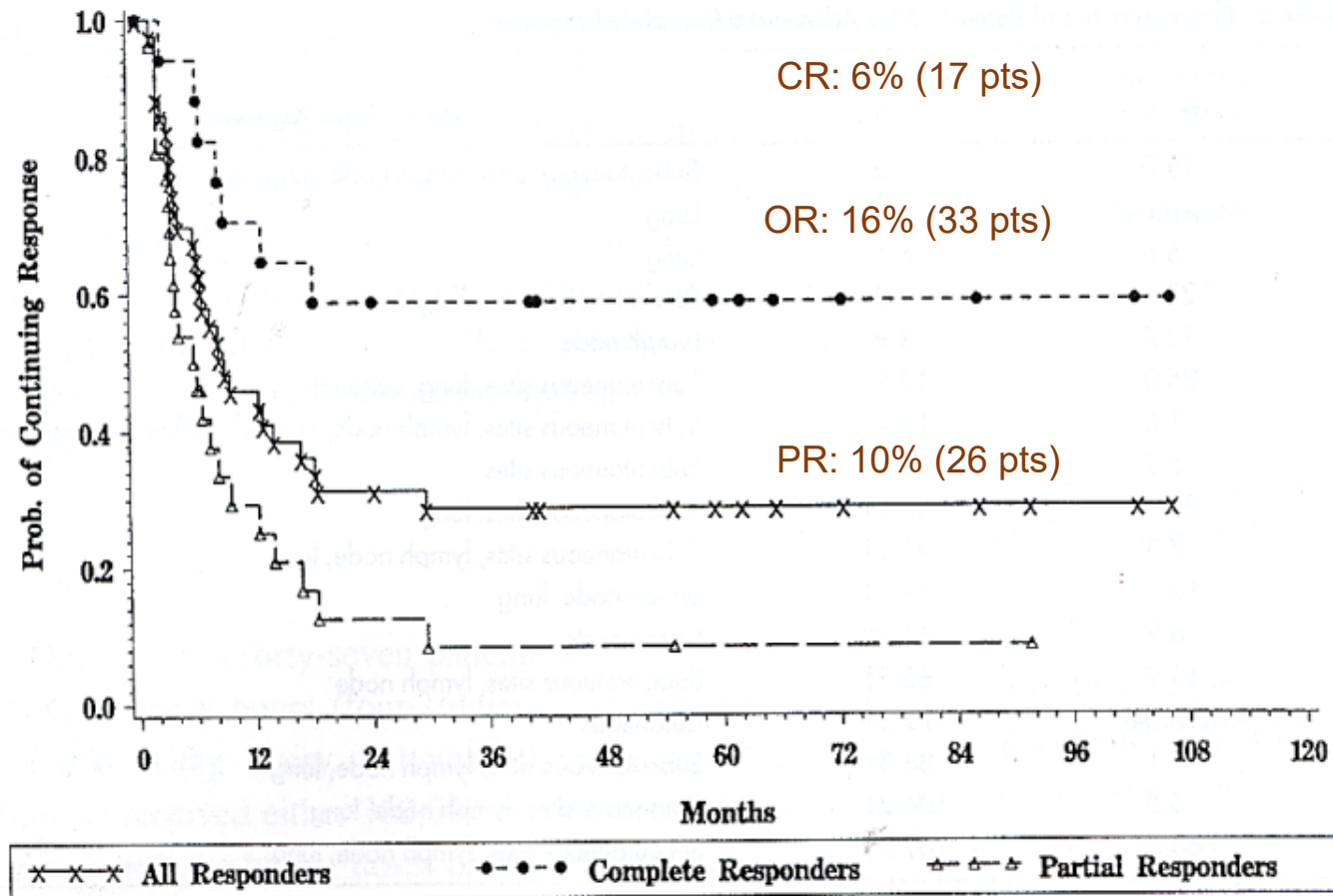


ULD IL-2 for GVHD prophylaxis: rationale

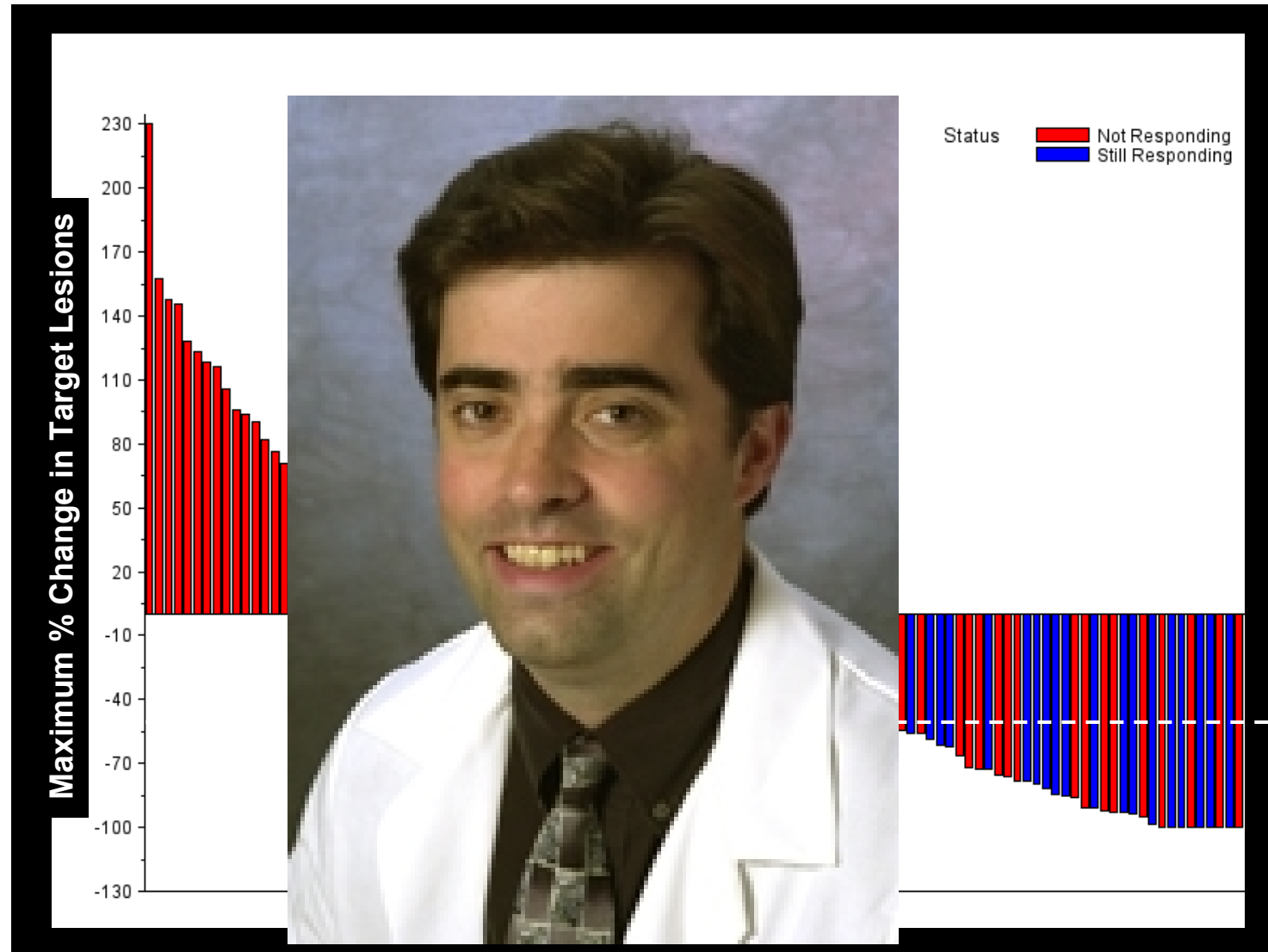
- **Ultra low dose IL-2**
 - Expands T_{regs} and NK cells
 - Effective for steroid refractory GVHD
 - Has been used for GVHD prophylaxis in matched donor SCT
- Quality and quantity of **regulatory T_{reg} and NK cells** impact haplo-SCT outcomes

*Koreth et al. N Engl J Med 2011; 365: 2055, Koreth et al. Blood 2016; 128: 130
Kennedy-Nasser, Ito S et al. Clin Cancer Res 2014; 20: 2215*

The Hallmark of IL-2 Therapy



Renal Cancer Response Rate=25% (n=118)



May 27, 2010 — Two white-coated cancer researchers are among the luminaries picked for *TIME* magazine's 2010 list of the 100 most influential people in the world. Larry Kwak, MD, PhD, and Doug Schwartzentruer, MD, FACS, join Sarah Palin, James Cameron, Steve Jobs, & Lady Gaga on this year's "influentials" list.

Dr. Doug Schwartzentruer



BiovaxID
patient-specific
vaccine for
follicular
lymphoma

Melanoma
gp100 2092M
+IL-2



Dr. Larry Kwak

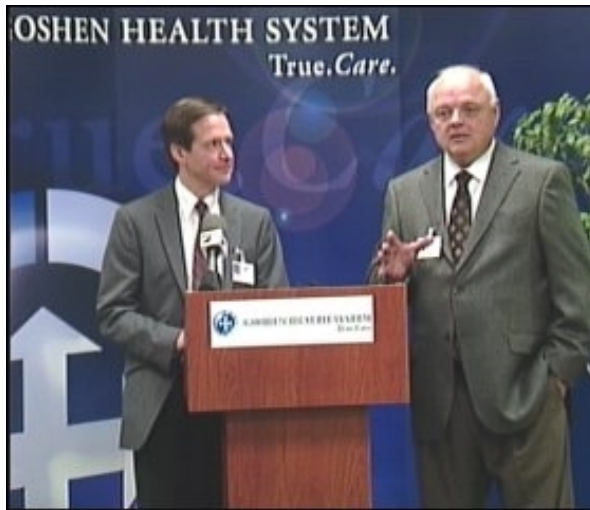
N Engl J Med 2011; June 2; 364:2119-27

The NEW ENGLAND JOURNAL of MEDICINE

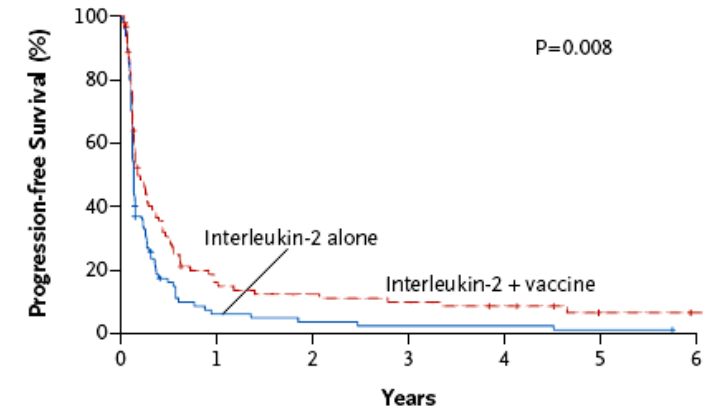
ORIGINAL ARTICLE

gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D.,



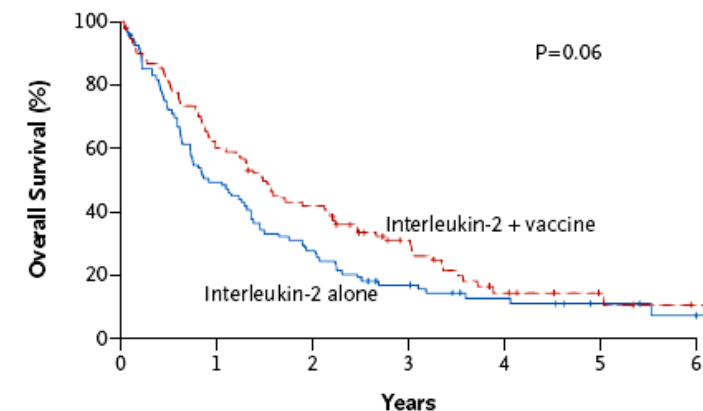
A Progression-free Survival



No. at Risk

Interleukin alone	94	5	3	2	2	1	0
Interleukin-2 + vaccine	91	13	10	8	6	2	1

B Overall Survival

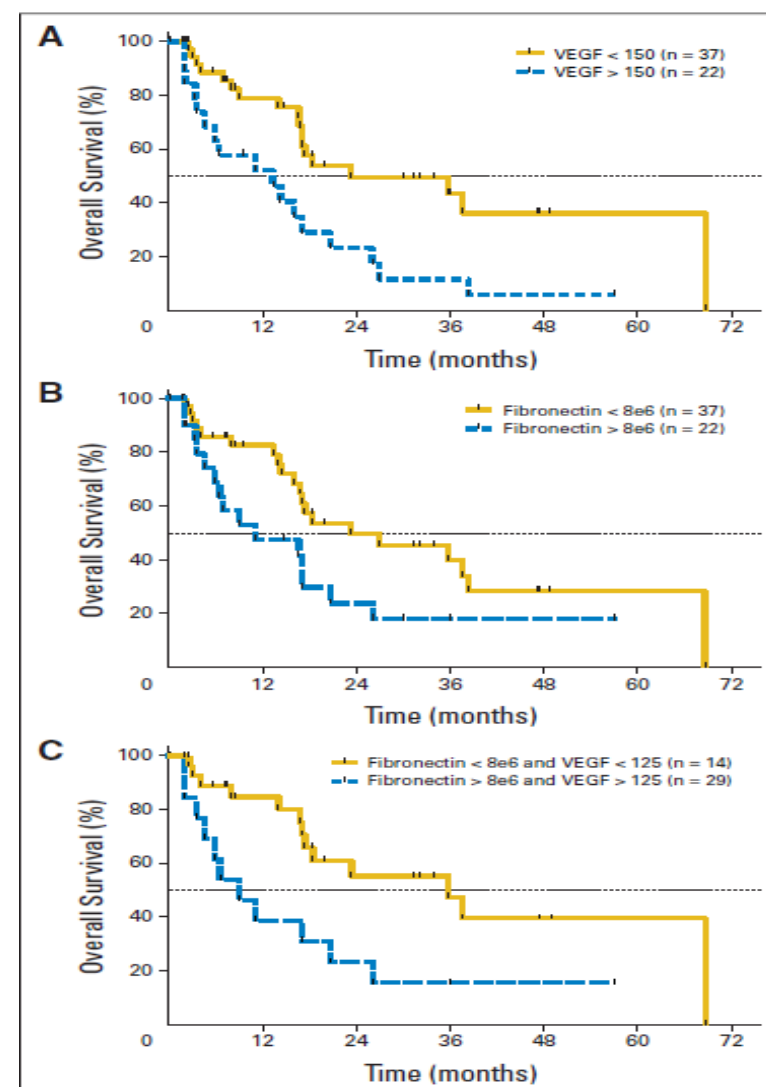
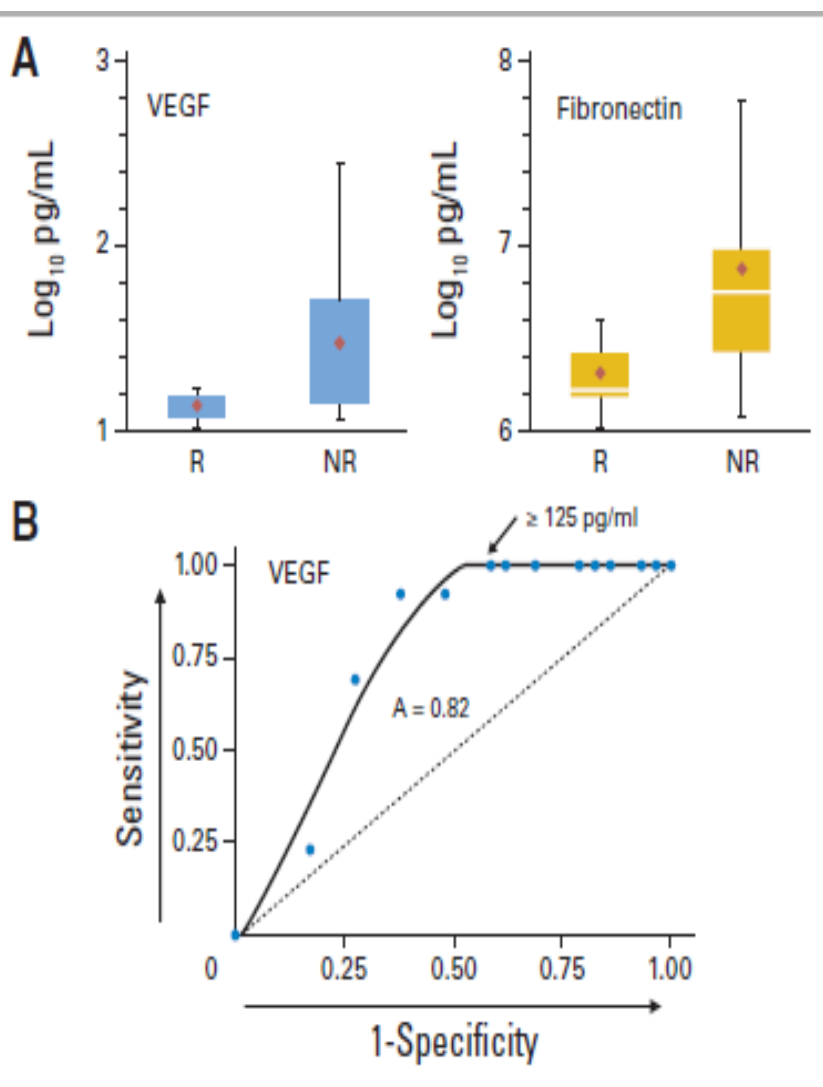


No. at Risk

Interleukin alone	94	46	26	14	8	4	1
Interleukin-2 + vaccine	91	54	37	20	8	4	1

Serum Vascular Endothelial Growth Factor and Fibronectin Predict Clinical Response to High-Dose Interleukin-2 Therapy

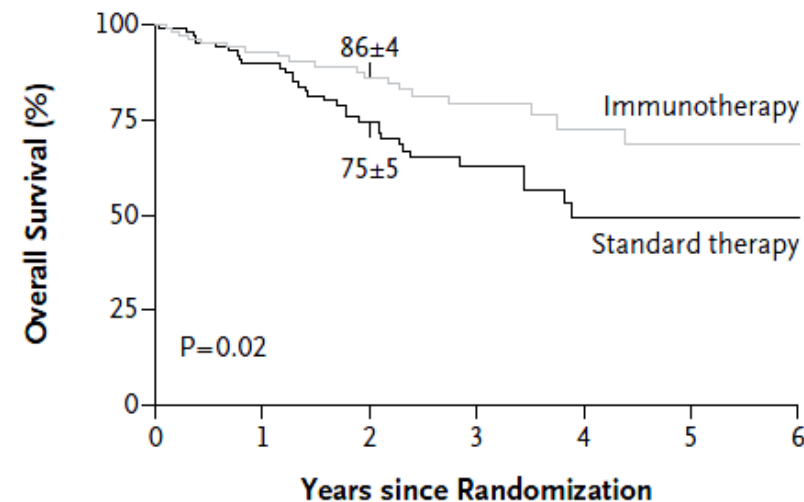
Marianna Sabatino, Seunghee Kim-Schulze, Monica C. Panelli, David Stronck, Ena Wang, Bret Taback, Dae Won Kim, Gail DeRaffele, Zoltan Pos, Francesco M. Marincola, and Howard L. Kaufman



ORIGINAL ARTICLE

Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma

Alice L. Yu, M.D., Ph.D., Andrew L. Gilman, M.D., M. Fevzi Ozkaynak, M.D., Wendy B. London, Ph.D., Susan G. Kreissman, M.D., Helen X. Chen, M.D., Malcolm Smith, M.D., Ph.D., Barry Anderson, M.D., Judith G. Villablanca, M.D., Katherine K. Matthay, M.D., Hiro Shimada, M.D., Stephan A. Grupp, M.D., Ph.D., Robert Seeger, M.D., C. Patrick Reynolds, M.D., Ph.D., Allen Buxton, M.S., Ralph A. Reisfeld, Ph.D., Steven D. Gillies, Ph.D., Susan L. Cohn, M.D., John M. Maris, M.D., and Paul M. Sondel, M.D., Ph.D.,
for the Children's Oncology Group



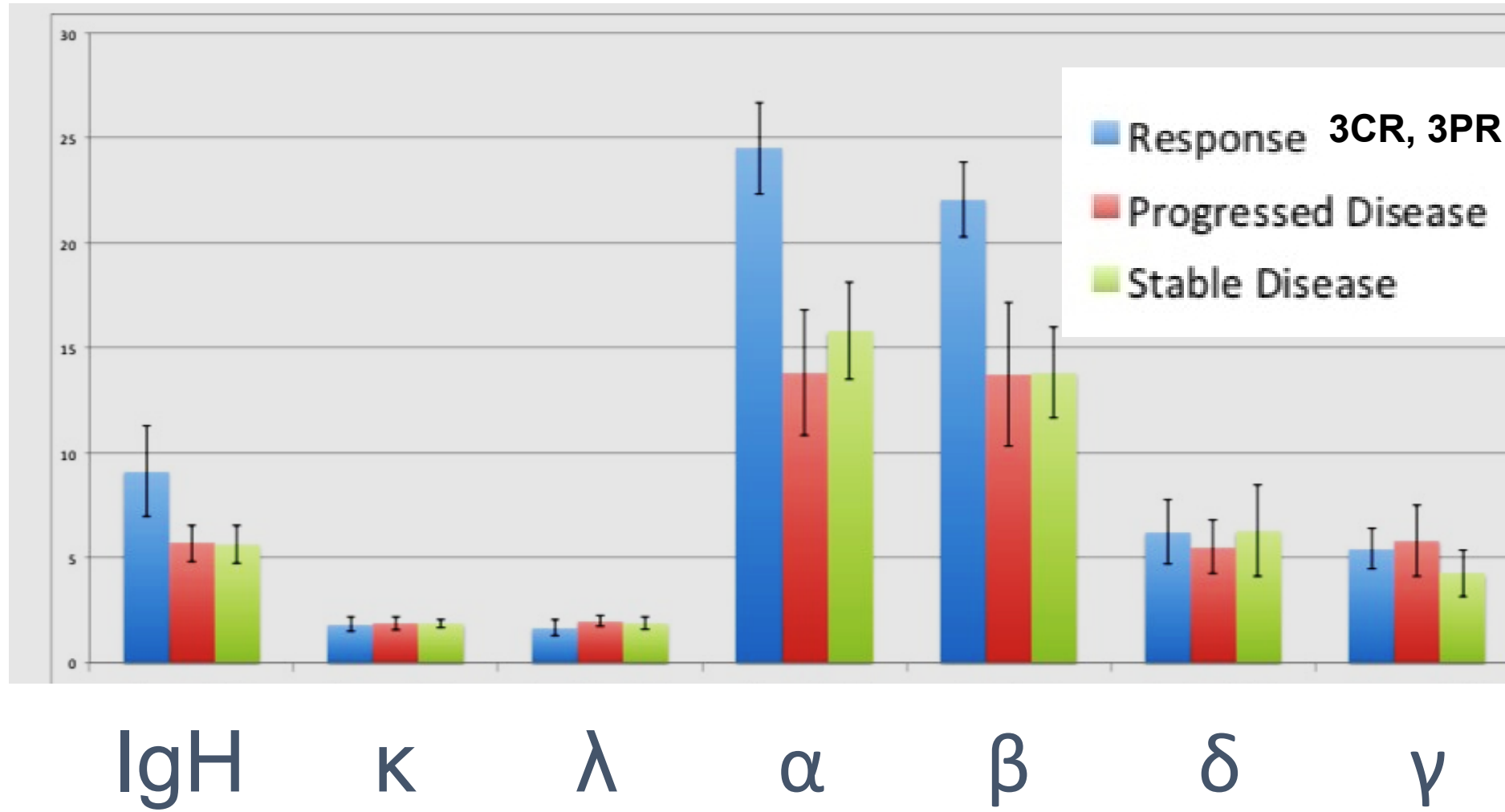
No. at Risk							
Immunotherapy	113	77	59	37	20	10	3
Standard therapy	113	79	51	26	12	9	1

The Strange Immunobiology of RCC

RESPONSE	INTEFERON α	IL- 2	CTLA4 AB	PD-1 AB	TIL
MELANOMA	+	+++	++	++	++++
RCC	+	+++	++	++	-

- 1: **Lotze MT**, Maranchie J, Appleman L. Inhibiting autophagy: a novel approach for the treatment of renal cell carcinoma. *Cancer J*. 2013 Jul-Aug;19(4):341-7
- 2: Romo de Vivar Chavez A, de Vera ME, Liang X, **Lotze MT**. The biology of IL-2 efficacy in the treatment of patients with RCC. *Med Oncol*. 2009; 1:3-12.
- 3: Bernhard H, Maeurer MJ, Jäger E, Wölfel T, Schneider J, Karbach J, Seliger B, Huber C, Storkus WS, **Lotze MT**, Meyer zum Büschenfelde KH, Knuth A. Recognition of human RCC and melanoma by HLA-A2-restricted CTL is mediated by shared peptide epitopes and up-regulated by IFN γ . *Scand J Immunol*. 1996;44:285-92.
- 4: Maeurer MJ, Martin DM, Castelli C, Elder E, Leder G, Storkus WJ, **Lotze MT**. Host immune response in RCC: IL-4 and IL-10 mRNA are frequently detected in freshly collected TIL. *Cancer Immunol Immunother*. 1995 Aug;41(2):111-21.
- 5: Spencer WF, Linehan WM, Walther MM, Haas GP, **Lotze MT**, Topalian SL, Yang JC, Merino MJ, Lange JR, Pockaj BA, et al. Immunotherapy with IL2 and IFN α in patients with metastatic RCC with *in situ* primary cancers. *J Urol*. 1992 147(1):24-30.
- 6: Rosenberg SA, **Lotze MT**, Muul LM, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant IL-2 to patients with metastatic cancer. *N Engl J Med*. 1985 Dec 5;313(23):1485-92.

D50 in 29 Advanced Renal Cancer Patients Treated with High Dose Interleukin 2 (IL-2) and Hydroxychloroquine Associated with Clinical Response



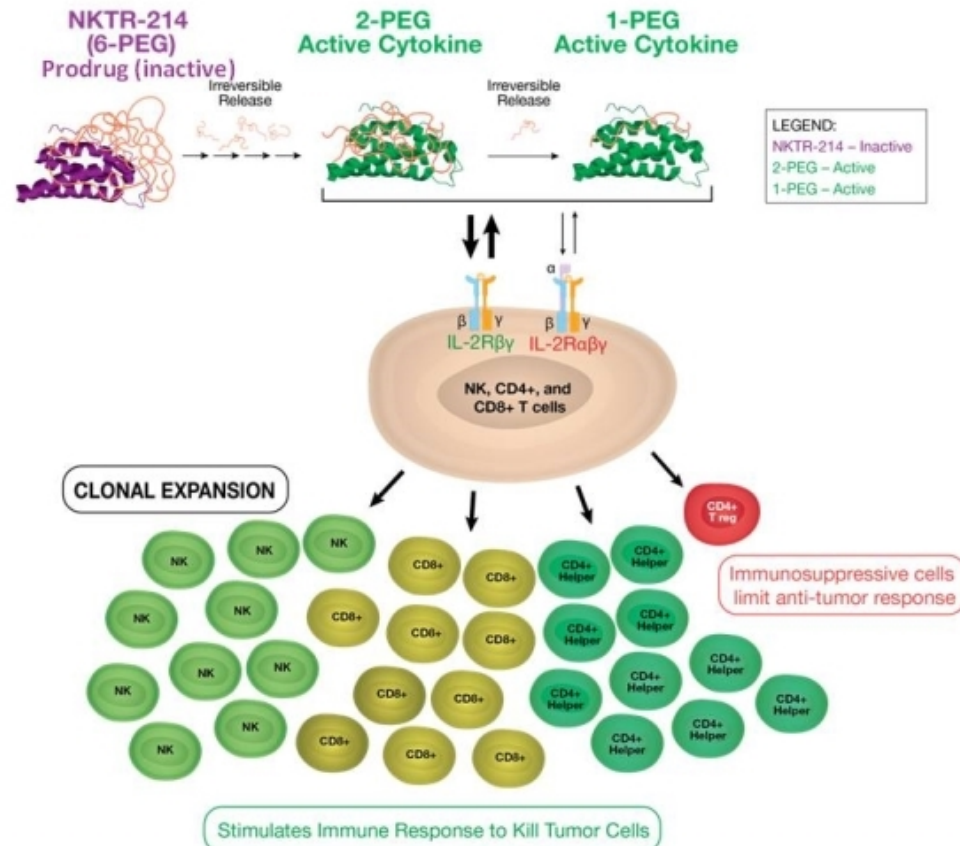
NKTR-214 (CD-122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT

ClinicalTrials.gov Identifier: NCT02983045

Adi Diab¹, Michael Hurwitz², Daniel Cho³, Vali Papadimitrakopoulou¹, Brendan Curti⁴, Scott Tykodi⁵, Igor Puzanov⁶, Nuhad K. Ibrahim¹, Sara M. Tolaney⁷, Debu Tripathy¹, Jianjun Gao¹, Arlene O. Siefker-Radtke¹, Wendy Clemens⁸, Mary Tagliaferri⁸, Scott N. Gettinger², Harriet Kluger², James M. G. Larkin⁹, Giovanni Grignani¹⁰, Mario Sznol², Nizar Tannir¹

¹The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²Yale School of Medicine, New Haven, CT, USA; ³NYU Medical Oncology Associates, New York, NY, USA; ⁴Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR, USA; ⁵University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ⁶Roswell Park Cancer Institute, Buffalo, NY, USA; ⁷Dana Farber Cancer Institute, Boston, MA, USA; ⁸Nektar Therapeutics, San Francisco, CA, USA; ⁹Royal Marsden NHS Foundation Trust London, United Kingdom; ¹⁰Candiolo Cancer Institute, Turin, Italy, Europe.

NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



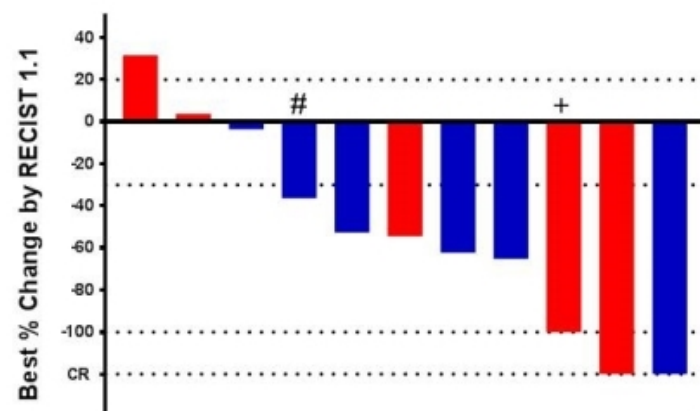
- NKTR-214 prodrug design with sustained signaling
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen administered every 3 week IV dosing
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- NKTR-214 increases proliferation of TILs and PD-1 expression on the surface of CD8+ T cells providing a mechanistic rationale for combining with nivolumab

Stage IV IO-Naïve 1L Melanoma Dose Escalation Cohort (N=11)

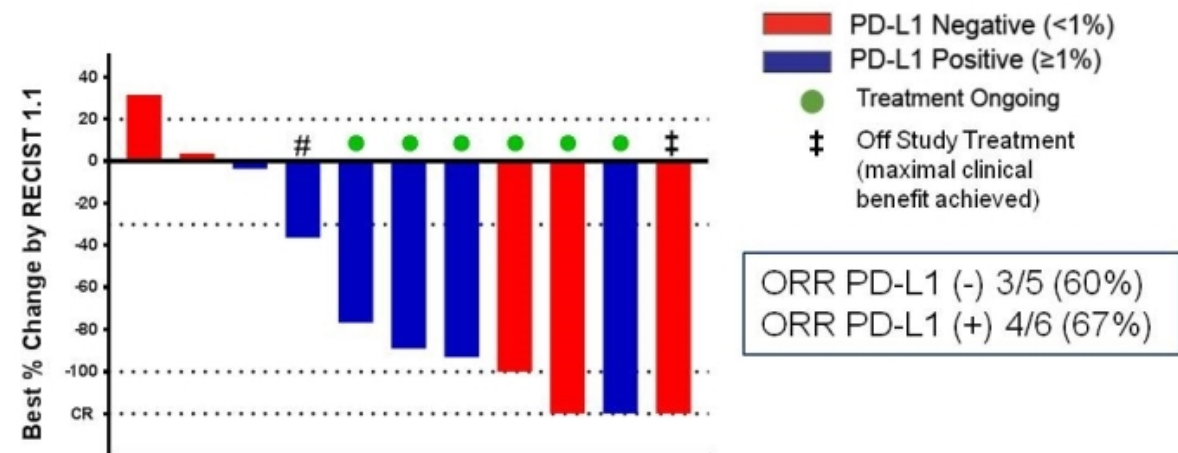
Deepening of Responses Over Time

Best Overall Response by RECIST: ORR=7/11 (64%); DCR=10/11 (91%)

SITC 2017 (Data Cut: Nov 2, 2017)



ASCO 2018 (Data Cut: May 29, 2018)



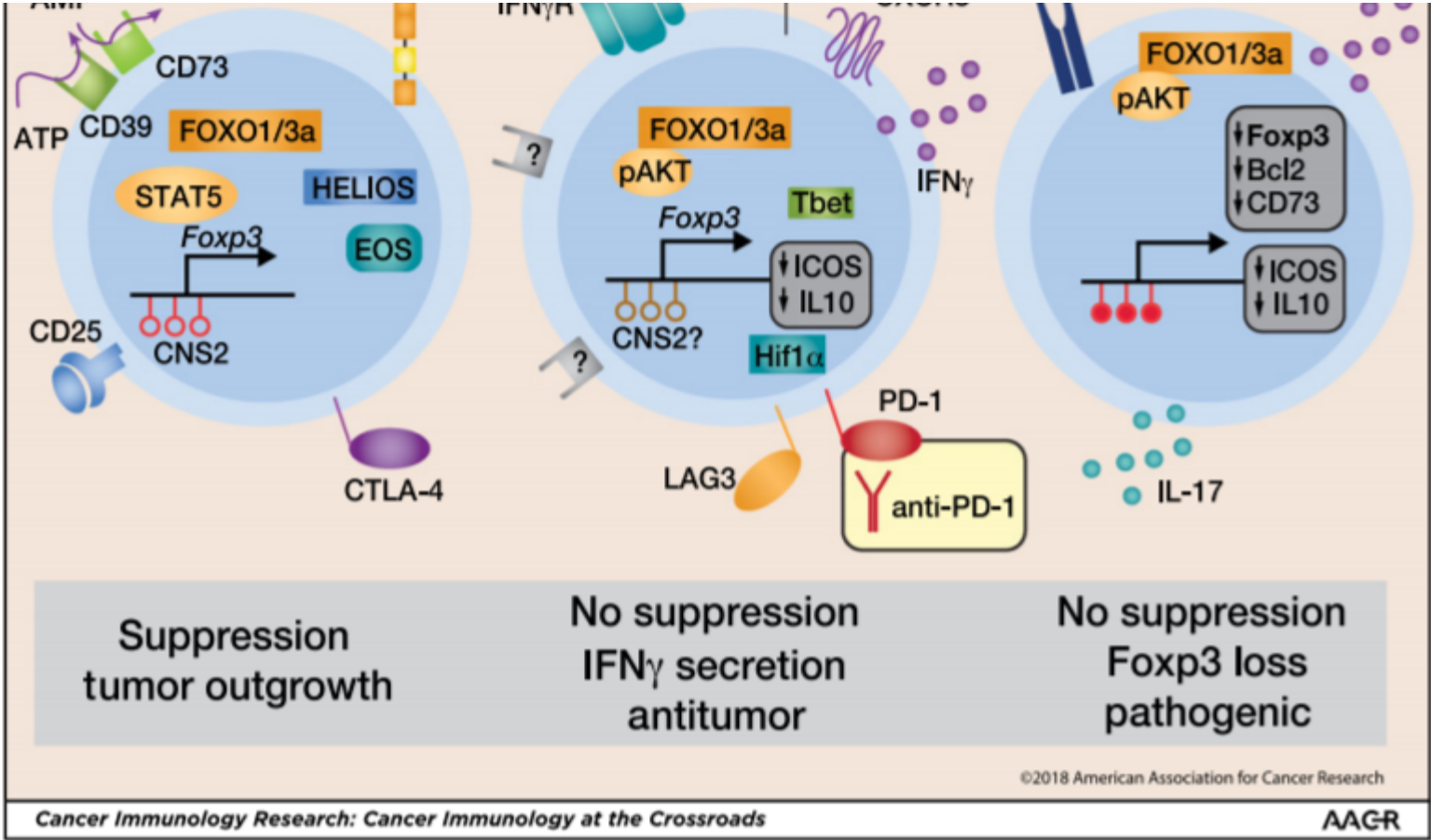
Treg Fragility: A Prerequisite for Effective Antitumor Immunity?

Abigail E. Overacre-Delgoffe and Dario A.A. Vignali

DOI: 10.1158/2326-6066.CIR-18-0066 Published August 2018

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IL2R beta-
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Alpdogan et al, *Blood* 2001;98:2256-226; Alpdogan et al, *J. Clin. Invest.* 2003; 112:1095–1107; Rosenberg et al, *J Immunother* 2006;29:313–319; Sportes et al, *J Exp Med* 2008; 205: 1710-1714; Levy et al, *J. Clin. Invest.* 2009; 119:997–1007; Sereti et al, *Blood* 2009; 113:6304-6314; Sportes et al, *Clin Cancer Res* 2010; 16: 727–735.

Administration of interleukin-7 after allogeneic bone marrow transplantation improves immune reconstitution without aggravating graft-versus-host disease

Onder Alpdogan, Cornelius Schmaltz, Stephanie J. Muriglan, Barry J. Kappel, Miguel-Angel Perales, Jimmy A. Rotolo, Jens A. Halm, Benjamin E. Rich, and Marcel R. M. van den Brink

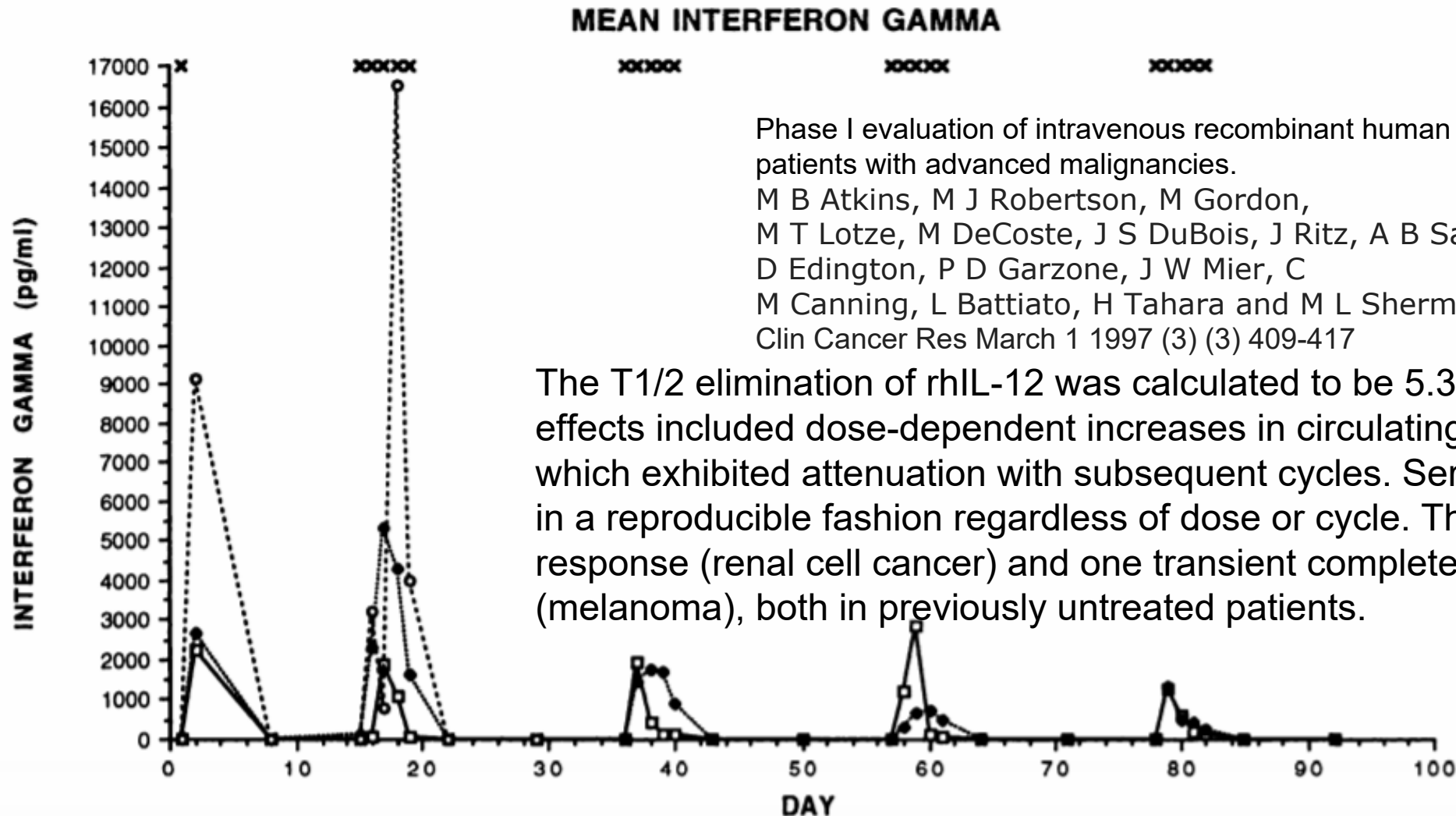
Alpdogan et al, Blood 2001;98:2256-226

IL-7 enhances peripheral T cell reconstitution after allogeneic hematopoietic stem cell transplantation

Önder Alpdogan, Stephanie J. Muriglan, Jeffrey M. Eng, Lucy M. Willis, Andrew S. Greenberg, Barry J. Kappel, and Marcel R.M. van den Brink

Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Phase I evaluation of intravenous recombinant human interleukin 12 in patients with advanced malignancies.



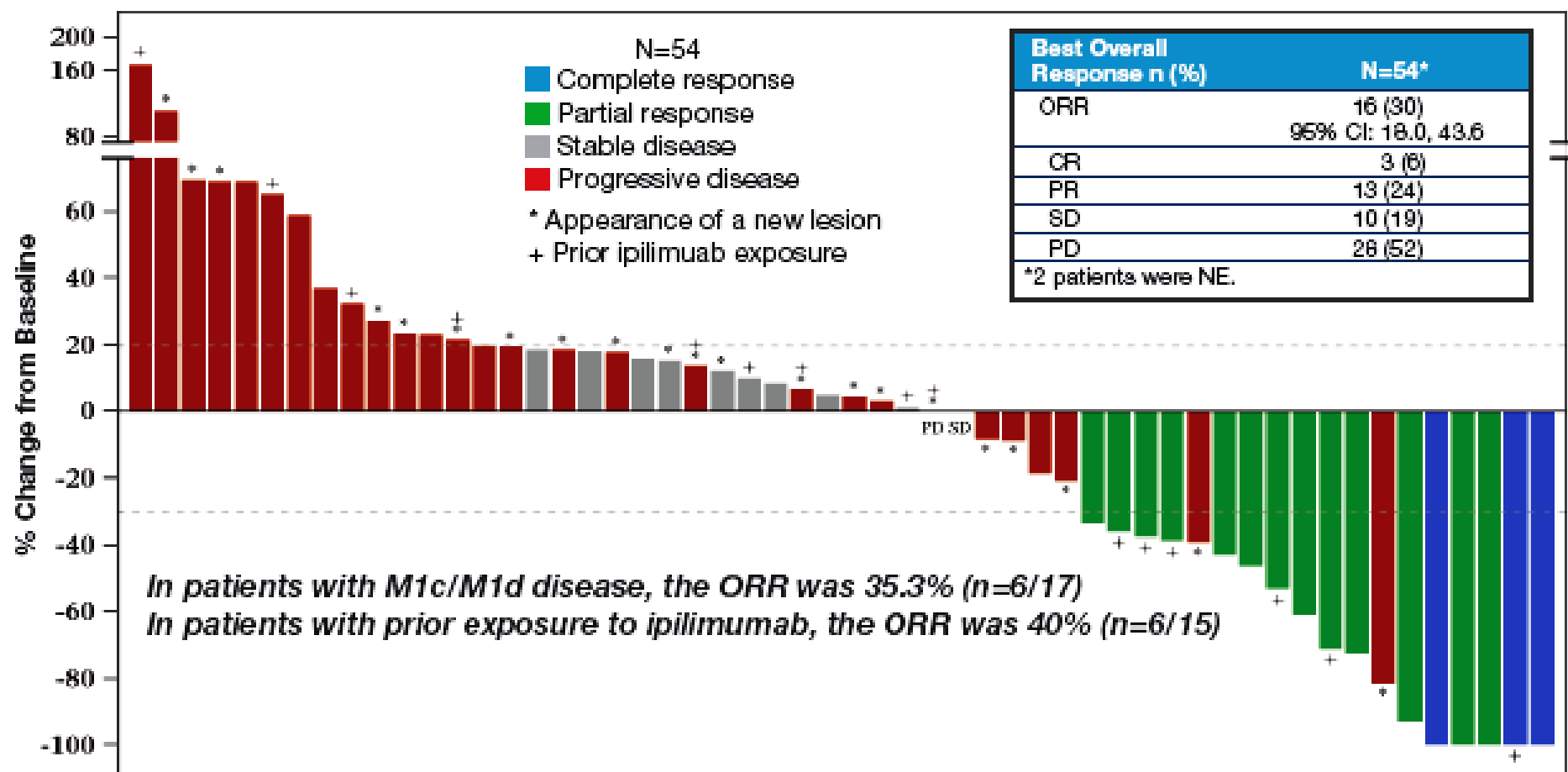
Phase I evaluation of intravenous recombinant human interleukin 12 in patients with advanced malignancies.

M B Atkins, M J Robertson, M Gordon,
M T Lotze, M DeCoste, J S DuBois, J Ritz, A B Sandler, H
D Edington, P D Garzone, J W Mier, C
M Canning, L Battiato, H Tahara and M L Sherman
Clin Cancer Res March 1 1997 (3) (3) 409-417

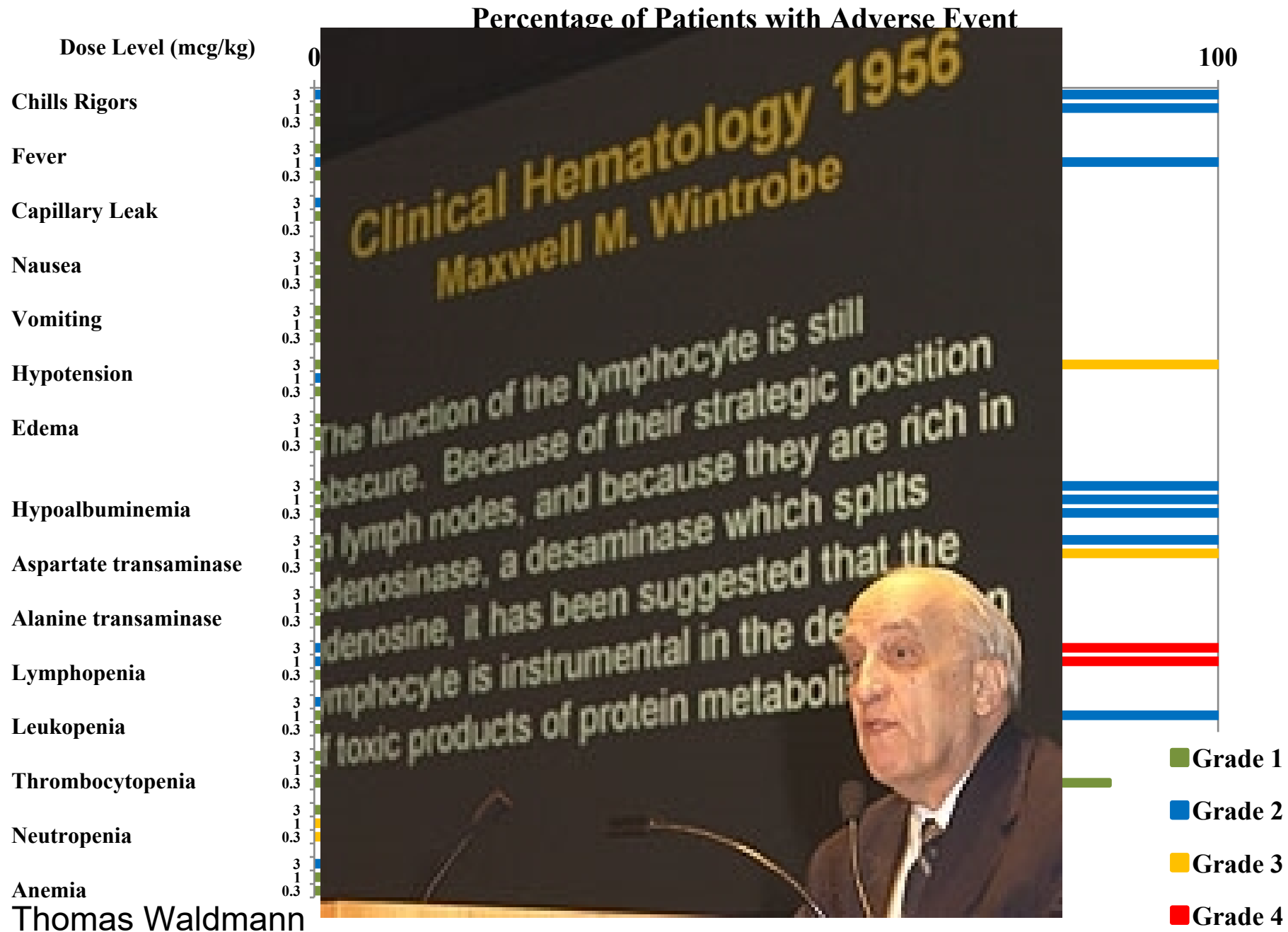
The T_{1/2} elimination of rhIL-12 was calculated to be 5.3-9.6 h. Biological effects included dose-dependent increases in circulating IFN-gamma, which exhibited attenuation with subsequent cycles. Serum neopterin rose in a reproducible fashion regardless of dose or cycle. There was one partial response (renal cell cancer) and one transient complete response (melanoma), both in previously untreated patients.

Durable responses and immune activation with intratumoral electroporation of pIL-12 plus pembrolizumab in actively progressing anti-PD-1 refractory advanced melanoma: KEYNOTE 695 interim data. SITC 2020

Figure 2. Best Overall Response



Interleukin 15 Adverse Event Summary



Cytokine Release and Adverse Events 3 mcg patients

