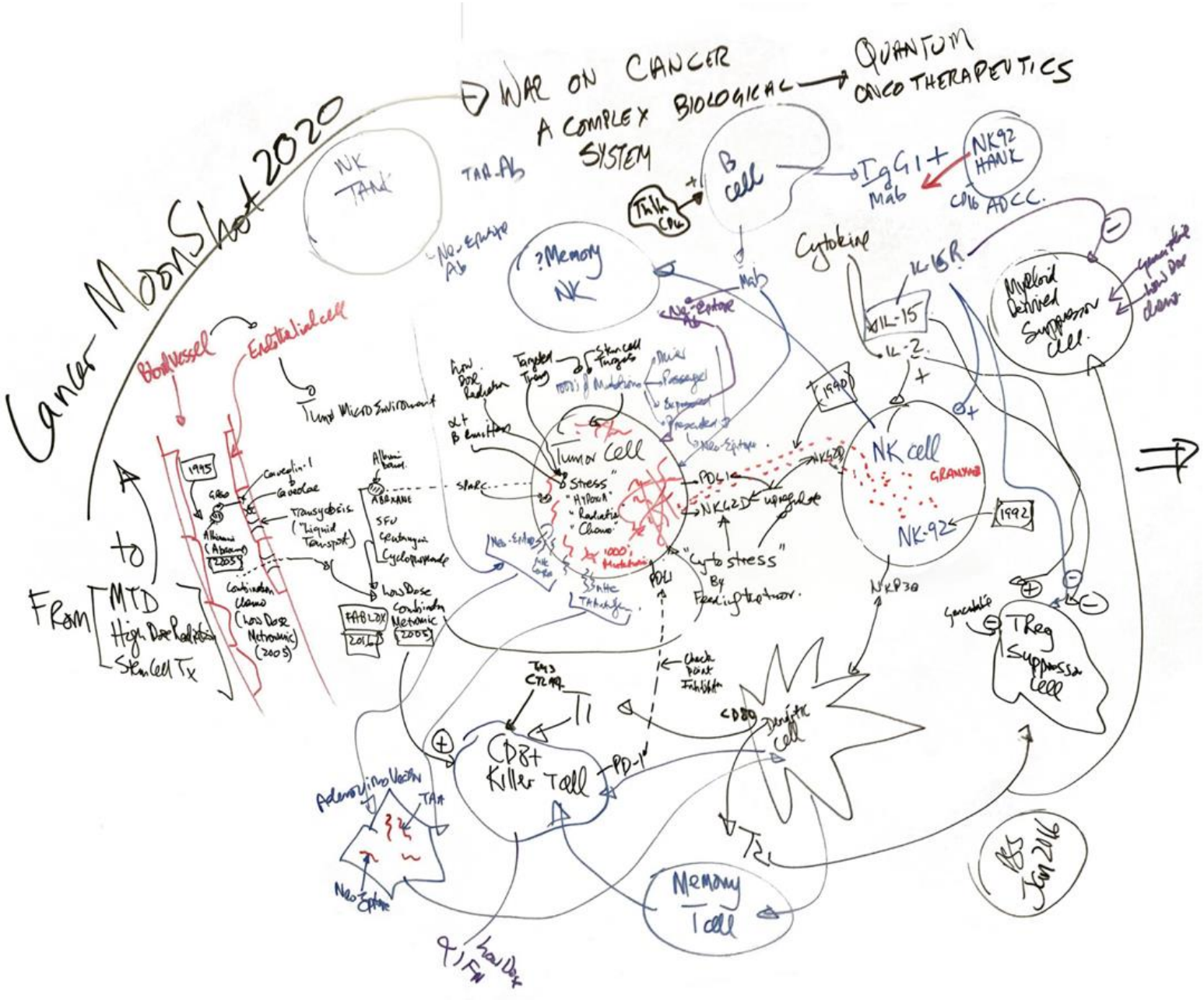
Winning the War Against Cancer: Harnessing the Power Within



“The Cancer Vaccine”

Hypothesis:
Orchestrating the innate and adaptive immune system drives immunogenic cell death with durable complete remission of cancer independent of tumor type

Presented to FDA, Oncology Center of Excellence (OCE) 2016

PSS Mind Map Jan 2016

The QUILT Trial 2016 – 2020 Testing the Hypothesis of the Cancer Vaccine

GPS Guided

Entering the Tumor Microenvironment + **Immunogenic Modulation Combination Therapy** + **Off-the-Shelf Natural Killer Cells** + **GPS Guided Cancer Vaccine** + **Fusion Proteins, Cytokine, Chemokine, Checkpoints** − **T-Regs, MDSC, M2**

- Transcytosis (Gp60) & FcRn
- Enhance Vascular Permeability (PEP)
- Tumor Necrosis Targeting (TNT)

- Low Dose Chemotherapy
- Low Dose Radiation
- Endocrine Deprivation
- Small-Molecule Inhibitors
- Monoclonal Antibody
- Fusion Proteins
- Checkpoint Inhibitors

NK

IL-15N72D
IL-15Rα
IgG1 Fc
N-803

LEK
CTLA4

MDSC
T-Reg
Macrophage

Multi-Clonal Cancer Cells → GPS → **Standard of Care** MTD

Surviving Cell Fraction
Immunogenic Modulated Cell Under Stress

Heterogenetic Resistant Tumor Clone

Tolerogenic Cell Death

Cold Tumor

Entering the tumor microenvironment

The Path to the Cancer Vaccine: QUILT Trial

Entering the Era of Clinical Genomics & Proteomics to Deliver Neoepitope Immunotherapy for N=1 (Patient's Own Control)

INNATE IMMUNOTHERAPY

Tumor Microenvironment Targeting & Immunomodulation

TNT
Gp60
FcRn
PEP

Natural Killer (NK) Cell

NKG2D
aNK
taNK

Immunogenic Cell Death
Direct Cell to Cell Contact

B-Cell

Antibodies to Tumor Associated Antigens
Antibodies to Neoepitope
NK
haNK

Immunogenic Cell Death
ADCC

ADAPTIVE IMMUNOTHERAPY

Immature Dendritic Cell

Neoantigens

Dendritic Cell Activation
Cancer Cell Vaccine

Cancer Vaccine

Adenovirus & Yeast Vectors

T-Cell Activation
TCR Co-Stimulation

Killer T-cell

Activated Killer T-cell

Immunogenic Cell Death
T-cell Mediated

Checkpoints Cytokines & Fusion Proteins (Fc)

MDSC
M2
Cytokine Stimulator
T-Reg
Checkpoint Inhibitor

Hot Tumor

Immunogenic Cell Death

Memory NK/T-Cell

Memory T & NK Cell

2/24/2026

January 2016 – Sharing Need for Paradigm Change With Scientific Thought Leaders

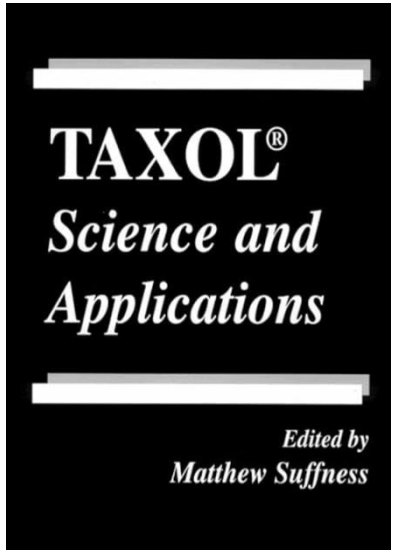
Lessons Learned After 55 Years of Cancer Drug Development and Standards of Care

Chemotherapy Development

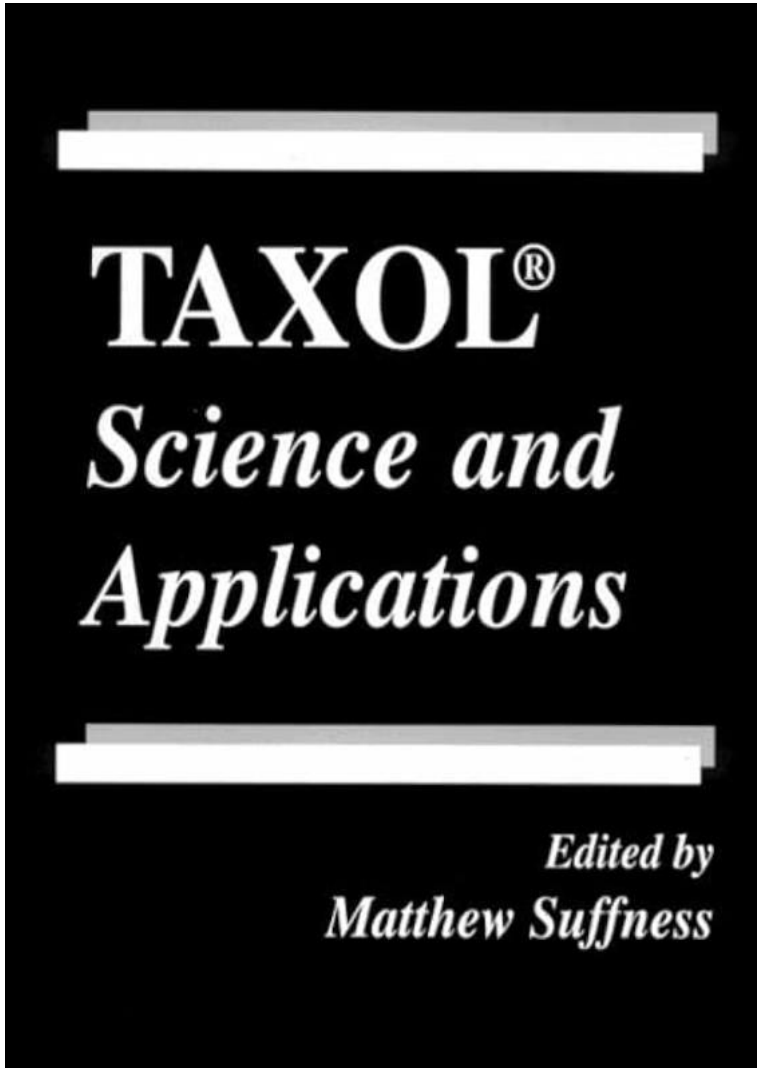
NCI Chemo Drug Discovery Based on Nude Athymic Mouse

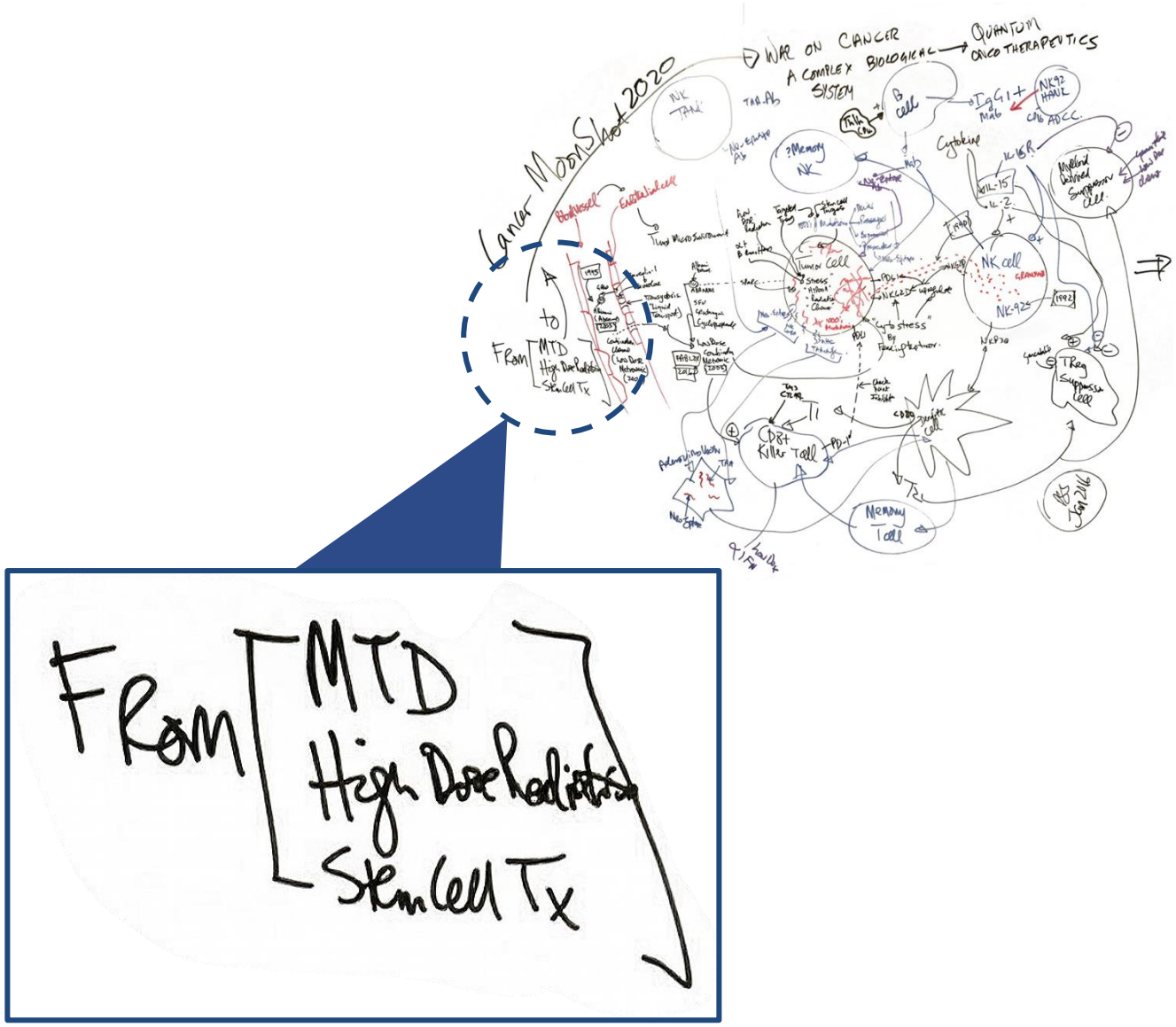
1966

"Flanagan reported the discovery of the 'nude' mouse in breeding experiments in 1966 and 2 years later it was reported that these animals were profoundly immunosuppressed due to the lack of a functional thymus gland… these mice could potentially be exactly what the NCI was looking for to develop human tumor models, but, since they lacked a functional immune system… for the NCI, the requirement was to produce enough mice to be able to test up to 500 drugs per year at multiple dose levels in multiple human tumor models."



Chemotherapy Drugs Developed Since 1966 Based on Models without an Immune System





Treatment Induced Lymphopenia

1994: High-Dose Chemotherapy Induces Lymphopenia

blood®

Volume 84, Issue 7, 1 October 1994, Pages 2221-2228

Article

Lymphocyte Depletion During Treatment With Intensive Chemotherapy for Cancer

Crystal L. Mackall, Thomas A. Fleisher, Margaret R. Brown, Ian T. Magrath, Aziza T. Shad, Marc E. Horowitz, Leonard H. Wexler, Melissa A. Adde, Linda L. McClure, Ronald E. Gress

1983: Radiation Induces Lymphopenia

J Clin Lab Immunol. 1983 Jul;11(3):159-60.

Radiotherapy and persistent reduction of peripheral T cells

B Petrini, J Wasserman, S Rotstein, H Blomgren

PMID: 6224938

Scientific Article

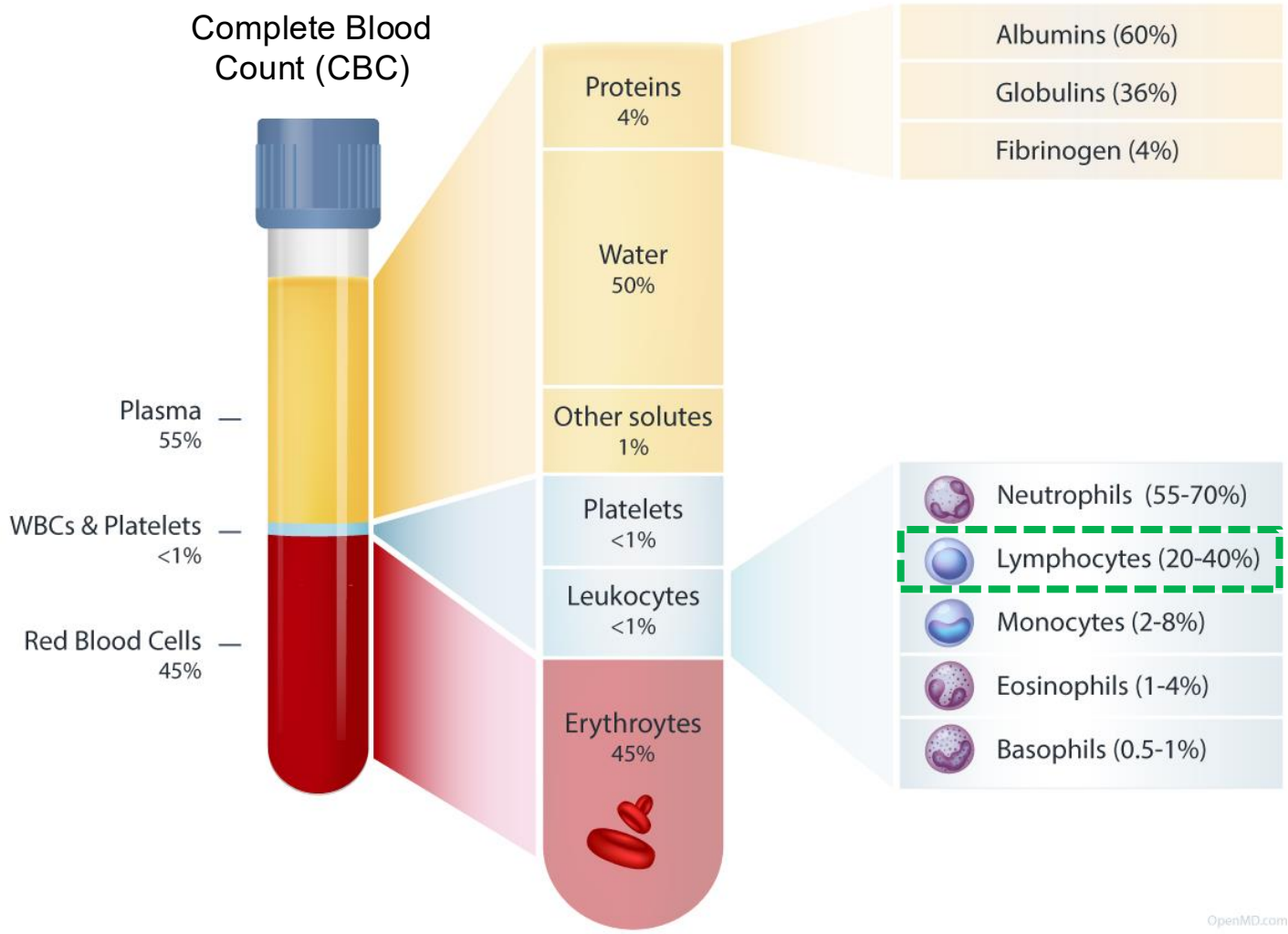
Meta-analysis and Critical Review: Association Between Radio-induced Lymphopenia and Overall Survival in Solid Cancers

Yasmine El Houat, MD,* Christophe Massard, MD, PhD, Veronique Quillien, MD, Renaud de Crevoisier, MD, PhD, and Joël Castelli, MD, PhD

Centre Eugène Marquis, Rennes, France

Received 16 June 2022; accepted 12 July 2022

The Missing Link: Lymphopenia is Measurable by Absolute Lymphocyte Count (ALC) with ICD Code Since 2015



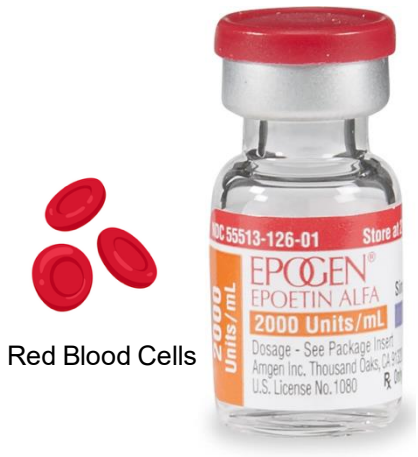
Severe Lymphopenia ALC <1,000

ICD Code:
D72.810
Oct 2015

The Treatment of Lymphopenia: The Missing Link

To Mitigate the Side Effects of Chemo & Radiation

To Treat **Anemia**
FDA Approved For All Cancers



Expands Red Blood Cells
To Deliver Oxygen

Red Blood Cell Count
RBC

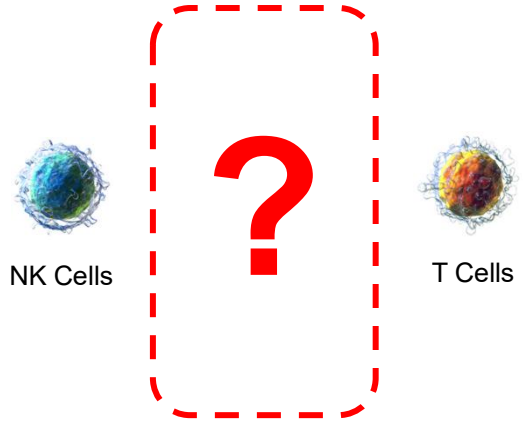
To Treat **Neutropenia**
FDA Approved For All Cancers

Expands Neutrophils
To Treat Infection

Absolute Neutrophil Count
ANC

The Missing Link

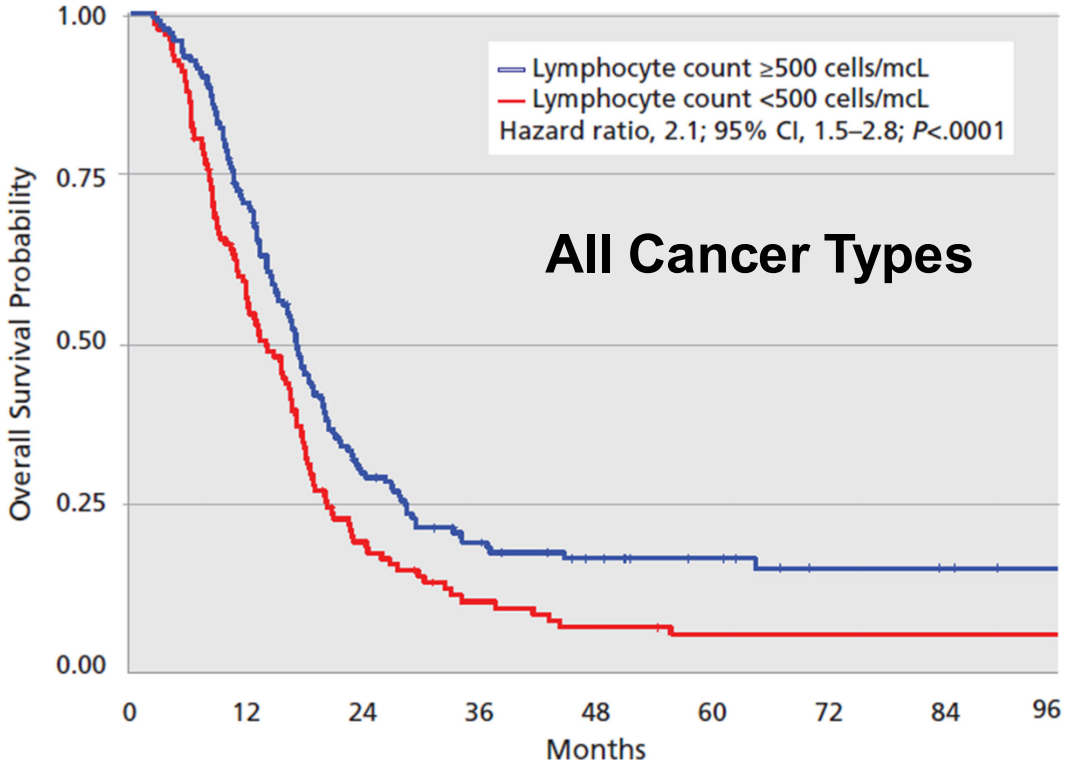
To Treat **Lymphopenia**



Absolute Lymphocyte Count
ALC

The Consequences of Lymphopenia in the US General Population and in Patients with Cancer ALC <1,500

2015: Chemo-Radiation Induced Lymphopenia Reduces Survival in All Tumor Types



HHS Public Access
Author manuscript
J Natl Compr Canc Netw. Author manuscript; available in PMC 2016 March 04.

Published in final edited form as:
J Natl Compr Canc Netw. 2015 October ; 13(10): 1225–1231.

Survival in Patients With Severe Lymphopenia Following Treatment With Radiation and Chemotherapy for Newly Diagnosed Solid Tumors

Stuart A. Grossman, MD[a], Susannah Ellsworth, MD[a], Jian Campian, MD, PhD[b], Aaron T.

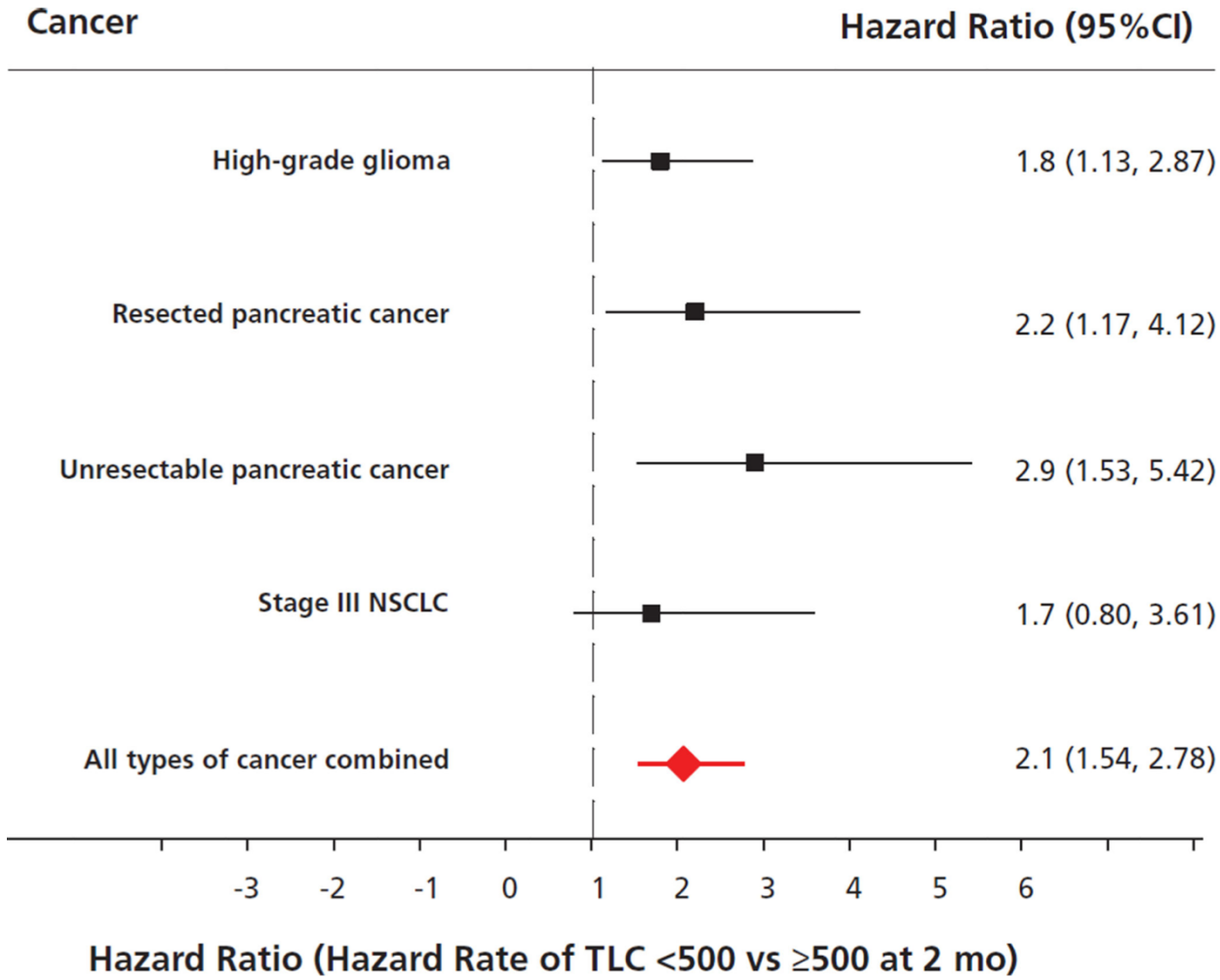


Figure 3.
Relationship between survival and grade III/IV treatment-related lymphopenia in 297 patients with solid tumors. Pooled hazard ratio, 2.1; 95% CI, 1.54–2.78; *P*<.0001.
Abbreviations: NSCLC, non–small cell lung cancer; TLC, total lymphocyte count.

2019: Excess Mortality Risk with Lymphopenia in the US General Population: "An Immunological Hazard in the General Population"

JAMA Network | Open™

2019

Original Investigation | Immunology

Association of Lymphopenia With Risk of Mortality Among Adults in the US General Population

David A. Zidar, MD, PhD; Sadeer G. Al-Kindi, MD; Yongmei Liu, MD, PhD; Nikolas I. Krieger, MS; Adam T. Perzynski, PhD; Michael Osnard, MD; Christopher Nmai, BA; Donald D. Anthony, MD; Michael M. Lederman, MD; Michael L. Freeman, PhD; Robert A. Bonomo, MD; Daniel I. Simon, MD; Jarrod E. Dalton, PhD

Abstract

IMPORTANCE Immune dysregulation can increase the risk of infection, malignant neoplasms, and cardiovascular disease, but improved methods are needed to identify and quantify immunologic hazard in the general population.

CONCLUSIONS AND RELEVANCE These findings suggest that lymphopenia is associated with reduced survival independently of and additive to traditional risk factors, especially when accompanied by altered erythropoiesis and/or heightened inflammation. Immune risk may be analyzed as a multidimensional entity derived from routine tests, facilitating precision medicine and population health interventions.

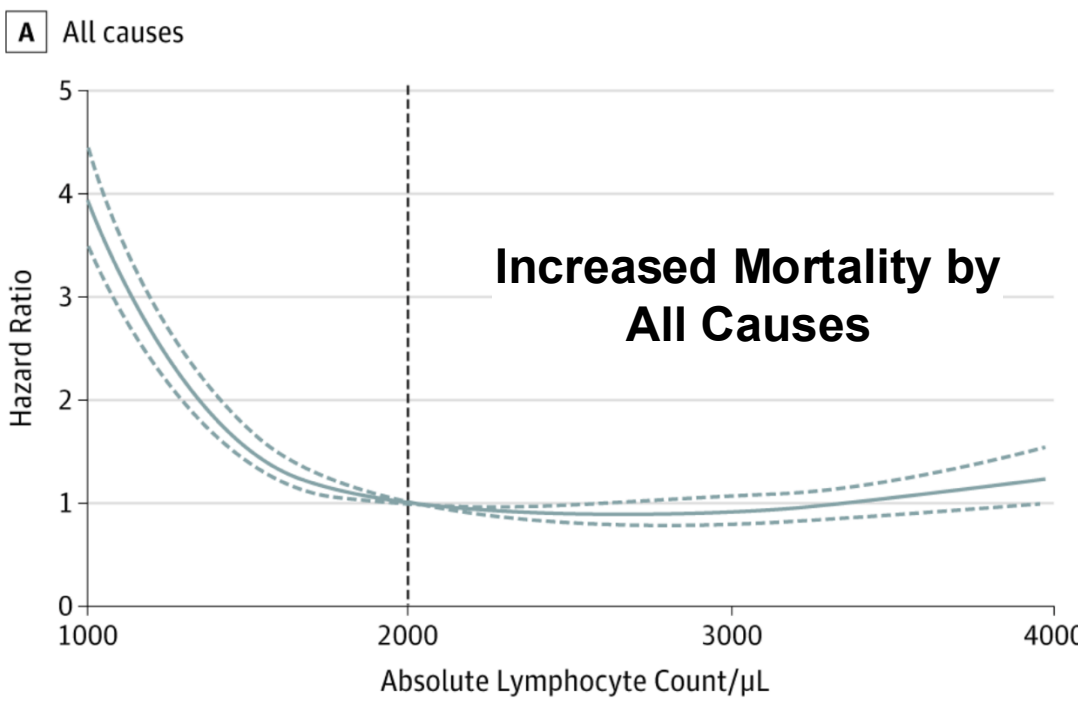
Key Points

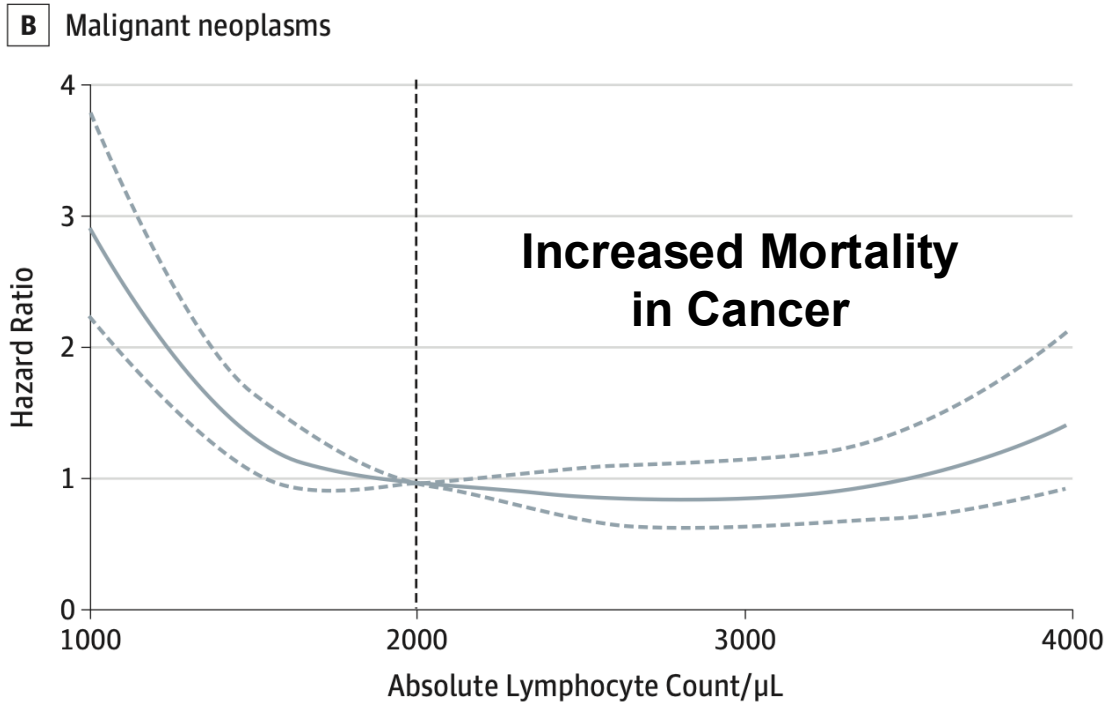
Question Are low lymphocyte levels associated with reduced survival in the general population?

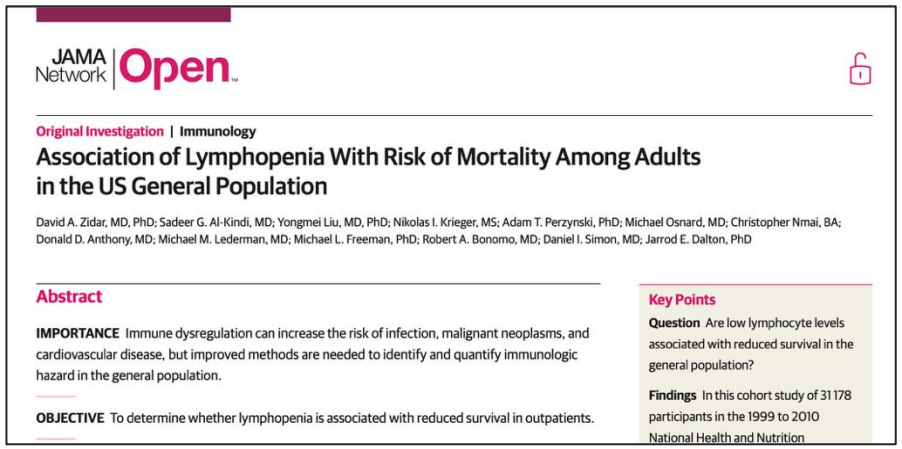
Findings In this cohort study of 31 178 participants in the 1999 to 2010 National Health and Nutrition Examination Survey, lymphopenia was associated with shortened survival independently of clinical variables, and this risk was further heightened when accompanied by abnormal hematologic (red blood cell distribution width) and/or inflammatory (C-reactive protein) parameters.

Meaning Based on these findings, patients with lymphopenia, especially those with other immunohematologic abnormalities, may have excess mortality risk; these patients are readily identifiable because tests of lymphocyte levels often occur during routine medical encounters.

2019 JAMA: Lymphopenia Consequences in US General Population







JAMA Network | Open

Original Investigation | Immunology

Association of Lymphopenia With Risk of Mortality Among Adults in the US General Population

David A. Zidar, MD, PhD; Sadeer G. Al-Kindi, MD; Yongmei Liu, MD, PhD; Nikolas I. Krieger, MS; Adam T. Perzynski, PhD; Michael Osnard, MD; Christopher Nmai, BA; Donald D. Anthony, MD; Michael M. Lederman, MD; Michael L. Freeman, PhD; Robert A. Bonomo, MD; Daniel I. Simon, MD; Jarrod E. Dalton, PhD

Abstract

IMPORTANCE Immune dysregulation can increase the risk of infection, malignant neoplasms, and cardiovascular disease, but improved methods are needed to identify and quantify immunologic hazard in the general population.

OBJECTIVE To determine whether lymphopenia is associated with reduced survival in outpatients.

Key Points

Question Are low lymphocyte levels associated with reduced survival in the general population?

Findings In this cohort study of 31 178 participants in the 1999 to 2010 National Health and Nutrition

Paradigm Change is Needed

"The root cause is the collapse of the immune system resulting in lymphopenia and cancer is merely the symptom"

2019

Ménétrier-Caux *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:85
https://doi.org/10.1186/s40425-019-0549-5

Journal for ImmunoTherapy of Cancer

REVIEW Open Access

Lymphopenia in Cancer Patients and its Effects on Response to Immunotherapy: an opportunity for combination with Cytokines?

Christine Ménétrier-Caux[1,2*], Isabelle Ray-Coquard[3], Jean-Yves Blay[1,3†] and Christophe Caux[1,2†]

Lymphopenia Across All Cancer Types

Table 1 Different published studies exploring the impact of the global lymphopenia or NK and T cell subsets on relapse-free survival (RFS) or overall survival (OS) in patients with solid tumors

Tumor Type	N	Type of lymphopenia evlauated	Lymphocyte Threshold (% lymphopenia)	RFS (Cox Analysis)			OS (Cox Analysis)			References
				RR	IC 95%	P value	RR	IC 95%	P value	
Sarcoma	193	Overall Lymphopenia	<1000 (24%)	Not evaluated			1.46	1.0-2.1	0.05	[68]
Ewing Sarcoma	24	Overall Lymphopenia	<500 (33%)	Not evaluated			4.34	1.35-14.28	0.007	[75]
Renal Cell Carcinoma	424	Overall Lymphopenia	≤1300 (28.06%)	Not evaluated			1.75	1.14-2.67	0.0102	[65]
Colon Carcinoma	260	Overall Lymphopenia	<1000 (19%)	1.56	1.0-2.43	0.048	2.35	2.34-4.14	0.003	[66]
Breast Carcinoma	195	Overall Lymphopenia	<1000 (28.7%)	1.82	1.27-2.59	0.001	2.23	1.36-3.65	0.001	[89]
Non Hodgkin Lymphoma	322	Overall Lymphopenia	<1000 (25%)	1.71	1.2-2.4	0.002	1.48	1.03-2.21	0.04	[68]
Diffuse large B cell lymphoma (DLBCL)	151	Overall Lymphopenia	≤1000 (35.8%)	Not evaluated			2.38	1.29-4.34	0.005	[90]
DLBCL	221	Overall Lymphopenia	<1000 (38.9%)	2.72	1.61-4.60	<0.001	2.51	1.38-4.58	0.003	[80]
DLBCL	89	Overall Lymphopenia	<840 (23%)	3.81	1.72-8.42	0.0009	4.38	1.88-13.28	0.0012	[79]
Follicular Lymphoma	228	Overall Lymphopenia	≤1000 (28%)	Not evaluated			1.72	1.33-2.24	$<10^{-4}$	[70]
Hodgkin Lymphoma	476	Overall Lymphopenia	<600 (18.06%)	1.59	0.96-2.58	0.06	1.25	0.74-2.15	0.4	[82]
Hodgkin Lymphoma	2497	Overall Lymphopenia	<600 (11%)	1.38		0.002	Not evaluated			[81]
Multiple Myeloma	537	Overall Lymphopenia	<1400 (62%)	Not evaluated			1.71	1.53-2.35	$<10^{-4}$	[92]
ATLL	60	Overall Lymphopenia	<1000 (35.6%)	1.93		0.004	2.37		0.0003	[93]
PTCLU	69	Overall Lymphopenia	<1000 (38%)	Not evaluated			4.0	1.9-8.3	$<10^{-4}$	[71]
PTCL-NOS	118	Overall Lymphopenia	1000 (30.5%)	1.94	1.19-3.18	0.008	2.24	1.33-3.78	0.002	[72]
Breast Carcinoma	287	Overall Lymphopenia	<1000 (27%)	1.48	1.1-2.0	0.01	1.8	1.3-2.4	0.0002	[68]
Breast Carcinoma	195	Overall Lymphopenia	<1000 (28.7%)	1.82	1.27-2.59	0.001	2.23	1.36-3.65	0.001	[89]
Breast Carcinoma 1st relapse	128	Overall Lymphopenia	<1000 (44.27%)	Not evaluated			1.8	1.15-2.82	0.01	[50][b]
Breast Carcinoma 1st relapse 1^{st} relapse	103	Overall Lymphopenia	<700 (22.3%)	Not evaluated			2.03	1.17-3.50	0.016	[21][b]
Breast Carcinoma 1st relapse 1^{st} relapse	103	$CD4^+$ Lymphopenia	≤450 (53.4%)	Not evaluated			2.50	1.57-3.98	$<10^{-4}$	[21][b]
Breast Carcinoma >2^{nd} relapse	101	$CD4^+$ Lymphopenia	≤450 (70.3%)	1.35	0.87-1.1	0.183	1.69	1.04-2.78	0.036	[21]
Metastatic Solid Tumors	219	$CD4^+$ Lymphopenia	≤450 (47.9%)	Not evaluated			1.5	1.1-2.1	0.017	[20]
Metastatic Solid Tumors	213	$CD4^+$ Lymphopenia	<450 (49.7%)	Not evaluated			7.7[a]	1.6-35[a]	0.007[a]	[19][a]
Non Hodgkin Lymphoma	88	$CD8^+$ Lymphopenia	<200	Not evaluated			3.30	1.21-9.0	0.01	[88]
Follicular Lymphoma	75	NK cells Lymphopenia	<150 (44%)	Not evaluated			6.73	0.76-59	0.08	[69]
DLBCL	136	NK cells Lymphopenia	≤80 (37.5%)	1.81	1.27-2.57	0.001	Not evaluated			[94]

[a] Analysis of the risk of early death; [b] Univariate analysis only

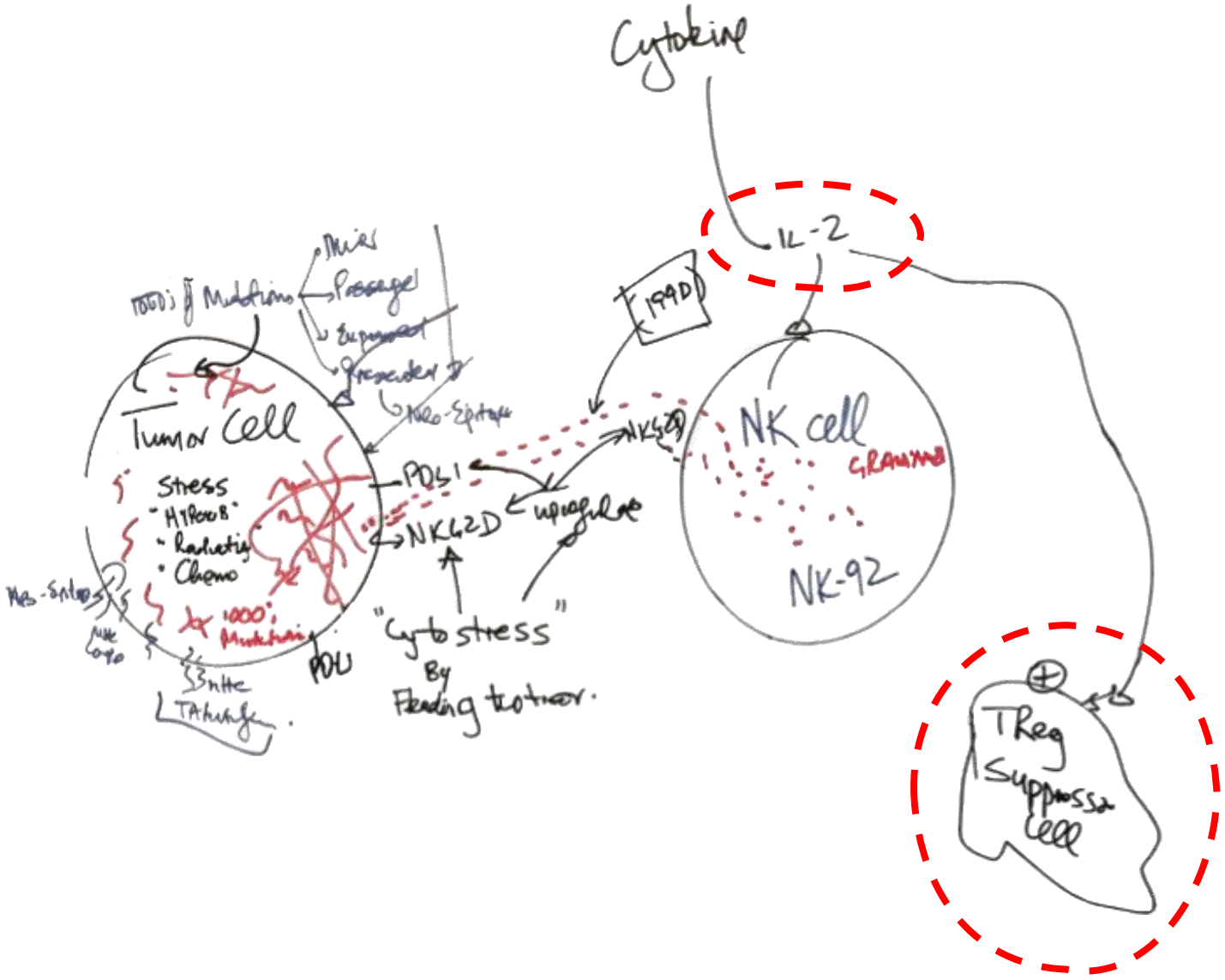
The Beginning of Immunotherapy 1992

Misconstruing the Treatment of Lymphopenia with IL-2

1992 to Present

IL-2 Misconstrued as a Key Cytokine for T Cell Growth

PROLEUKIN® (aldesleukin), a recombinant form of interleukin-2 (IL-2)



IL-2 Still Misconstrued as a Key Cytokine for T Cell Growth

2017

PLOS ONE

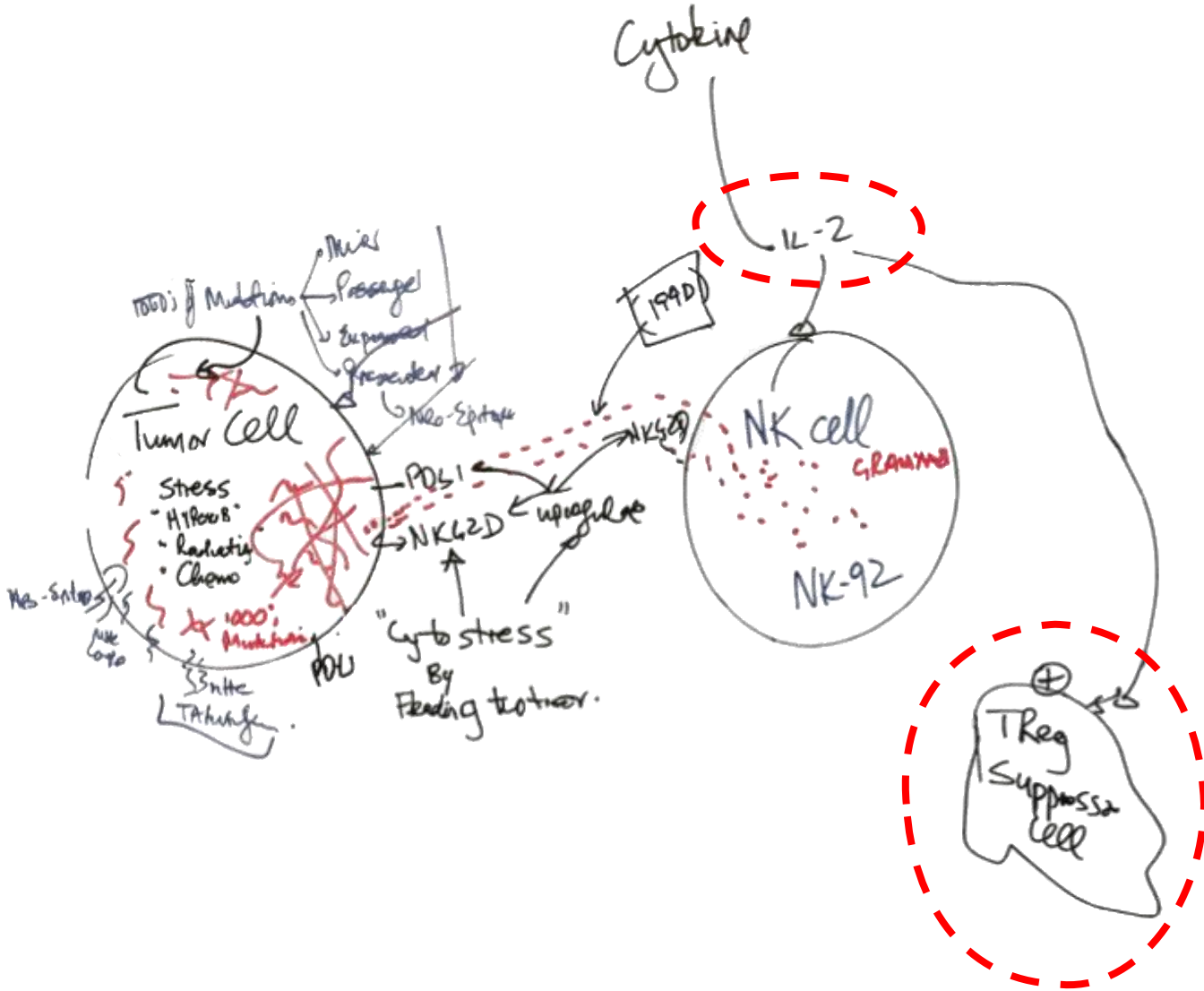
RESEARCH ARTICLE

Modeling the receptor pharmacology, pharmacokinetics, and pharmacodynamics of NKTR-214, a kinetically-controlled interleukin-2 (IL2) receptor agonist for cancer immunotherapy

Deborah Charych☯*, Samira Khalili☯, Vidula Dixit, Peter Kirk, Thomas Chang, John Langowski, Werner Rubas, Stephen K. Doberstein, Michael Eldon, Ute Hoch, Jonathan Zalevsky

Nektar Therapeutics, San Francisco, California, United States of America

☯ These authors contributed equally to this work.
* DCharych@nektar.com



Realization of the Innate Power of IL-15

2006: Scientific Insight into the Difference Between IL-2 and IL-15

2006

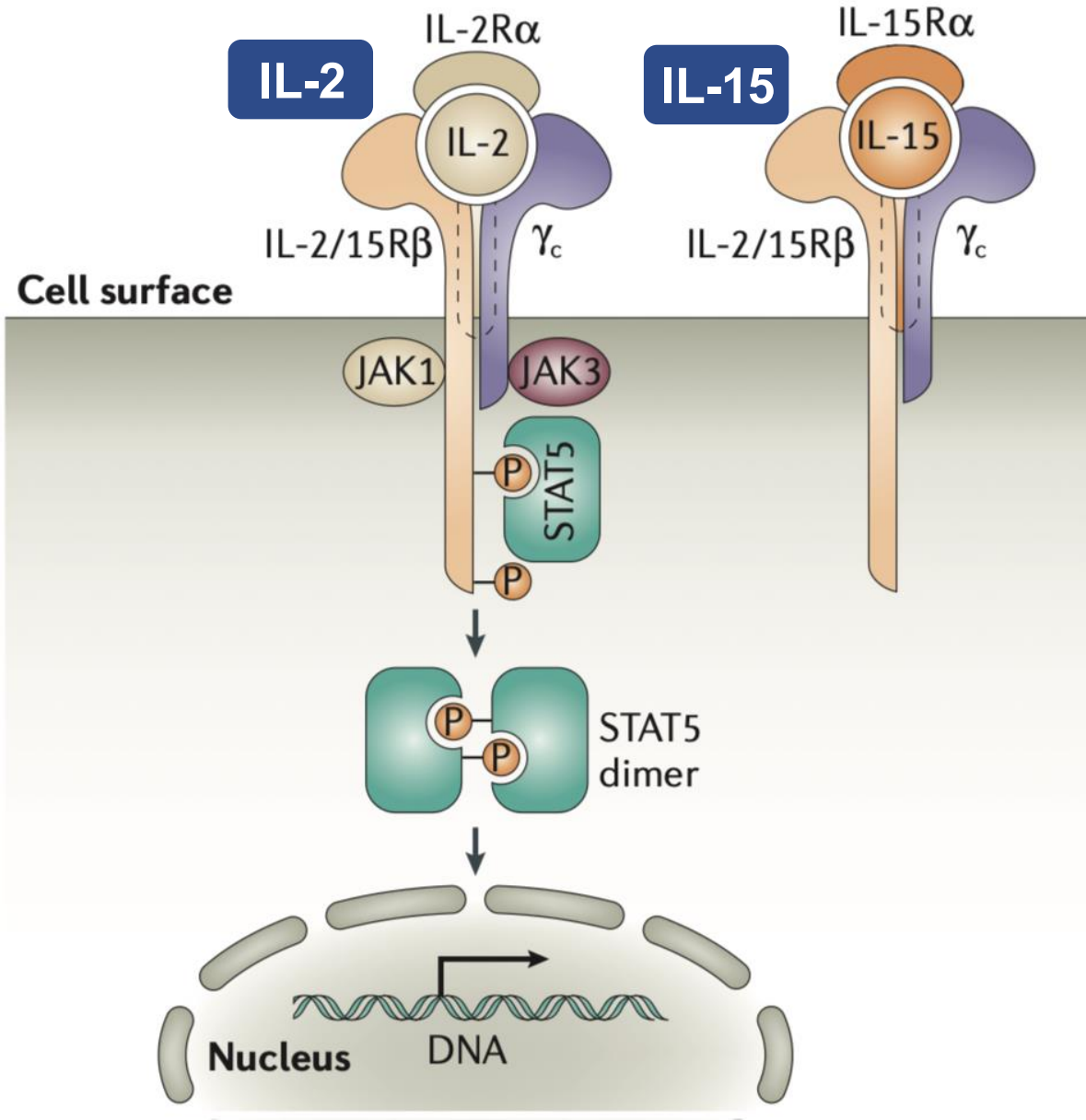
nature REVIEWS IMMUNOLOGY

The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design

Thomas A. Waldmann

Abstract | Interleukin-2 and interleukin-15 have pivotal roles in the control of the life and death of lymphocytes. Although their heterotrimeric receptors have two receptor subunits in common, these two cytokines have contrasting roles in adaptive immune responses. The unique role of interleukin-2 is in the elimination of self-reactive T cells to prevent autoimmunity. By contrast, interleukin-15 is dedicated to the prolonged maintenance of memory T-cell responses to invading pathogens. As discussed in this Review, the biology of these cytokines will affect the development of novel therapies for malignancy and autoimmune diseases, as well as the design of vaccines against infectious diseases.

Thomas A. Waldmann, M.D.
(1930-2021)



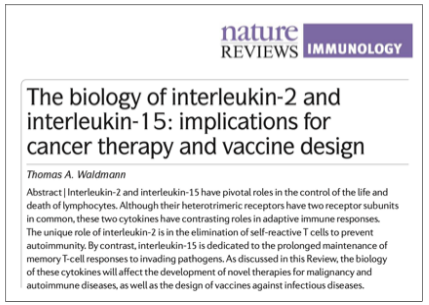
Key Points

- In many adaptive immune responses, IL-2 and IL-15 have distinct, and often competing, actions. IL-2 has a role in activation-induced cell death and in maintenance of regulatory T cells. In this way, it is involved in the elimination of self-reactive T cells, which if left unregulated could lead to the development of autoimmune diseases. By contrast, IL-15 is pivotal in the maintenance of long-lasting, high-avidity $CD8^+$ memory T cells that are involved in the elimination of invading pathogens, thereby protecting the host against infection.

- IL-2 is a secreted cytokine and binds pre-formed heterotrimeric receptors on the surface of activated cells. By contrast, IL-15 is mainly membrane bound, and it induces signaling in the context of cell–cell contact, at the immunological synapse. The unique subunit of the IL-15R, IL-15Rα, presents IL-15 *in trans* to neighboring natural killer (NK) cells and $CD8^+$ T cells.

- IL-15 activates T cells and NK cells and has a role in persistence of $CD8^+$ memory T cells. It therefore might be better than IL-2 for the treatment of cancer and as a component of molecular vaccines against infectious diseases.

2006


nature REVIEWS IMMUNOLOGY

The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design

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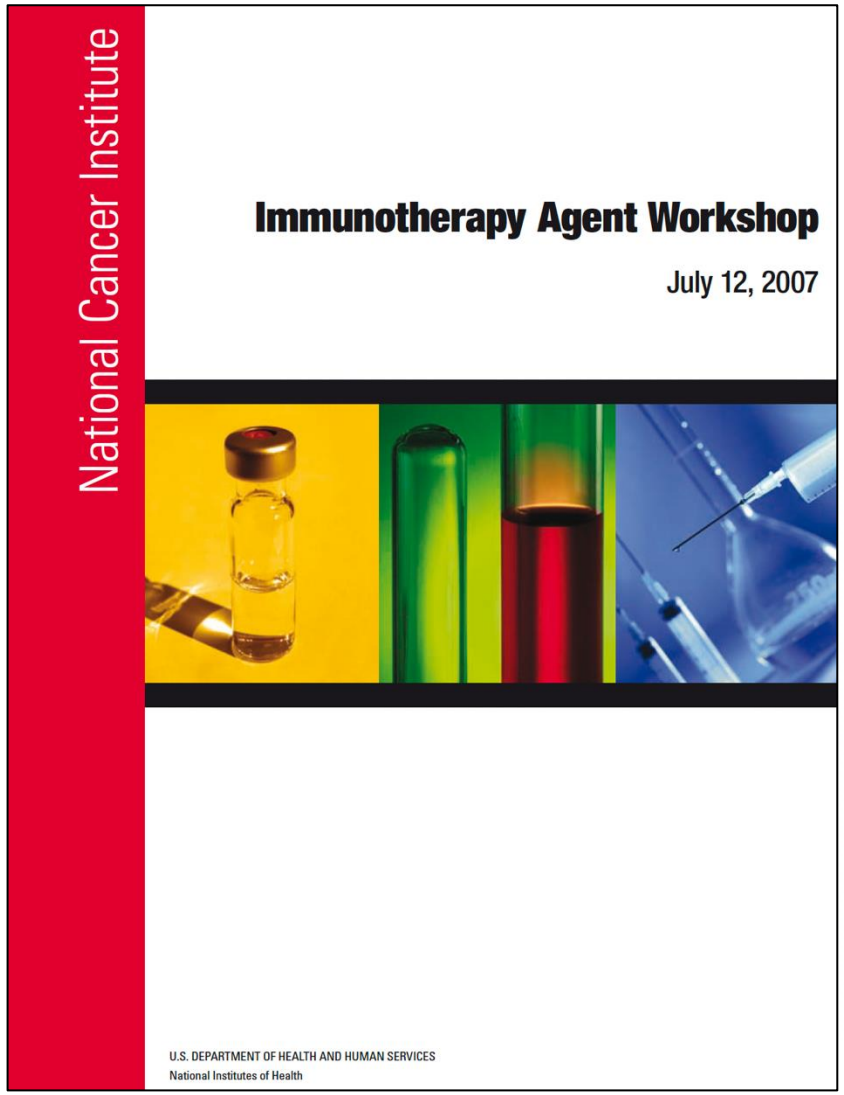
Abstract | Interleukin-2 and interleukin-15 have pivotal roles in the control of the life and death of lymphocytes. Although their heterotrimeric receptors have two receptor subunits in common, these two cytokines have contrasting roles in adaptive immune responses. The unique role of interleukin-2 is in the elimination of self-reactive T cells to prevent autoimmunity. By contrast, interleukin-15 is dedicated to the prolonged maintenance of memory T-cell responses to invading pathogens. As discussed in this Review, the biology of these cytokines will affect the development of novel therapies for malignancy and autoimmune diseases, as well as the design of vaccines against infectious diseases.

Thomas A. Waldmann, M.D.
(1930-2021)

2007: NCI Immunotherapy Workshop to Identify Molecules to Cure Cancer



NATIONAL CANCER INSTITUTE
IMMUNOTHERAPY AGENT WORKSHOP
JULY 12TH, 2007

EXECUTIVE SUMMARY

Twenty agents are presented on the list, presented in rank order. However, all are considered to have substantial potential for cancer therapy. Criteria essential for inclusion on the list included:

- Potential for use in cancer therapy.
- Perceived need by multiple, independent clinical investigators.
- Potential use in more than one clinical setting (i.e., against different tumor types or as part of multiple therapy regimens).
- Not broadly available for testing in patients.
- Not commercially available or likely to be approved for commercial use in the near future.

2007: IL-15 Identified as the Key Cytokine (T Cell Growth Factor) to Cure Cancer!

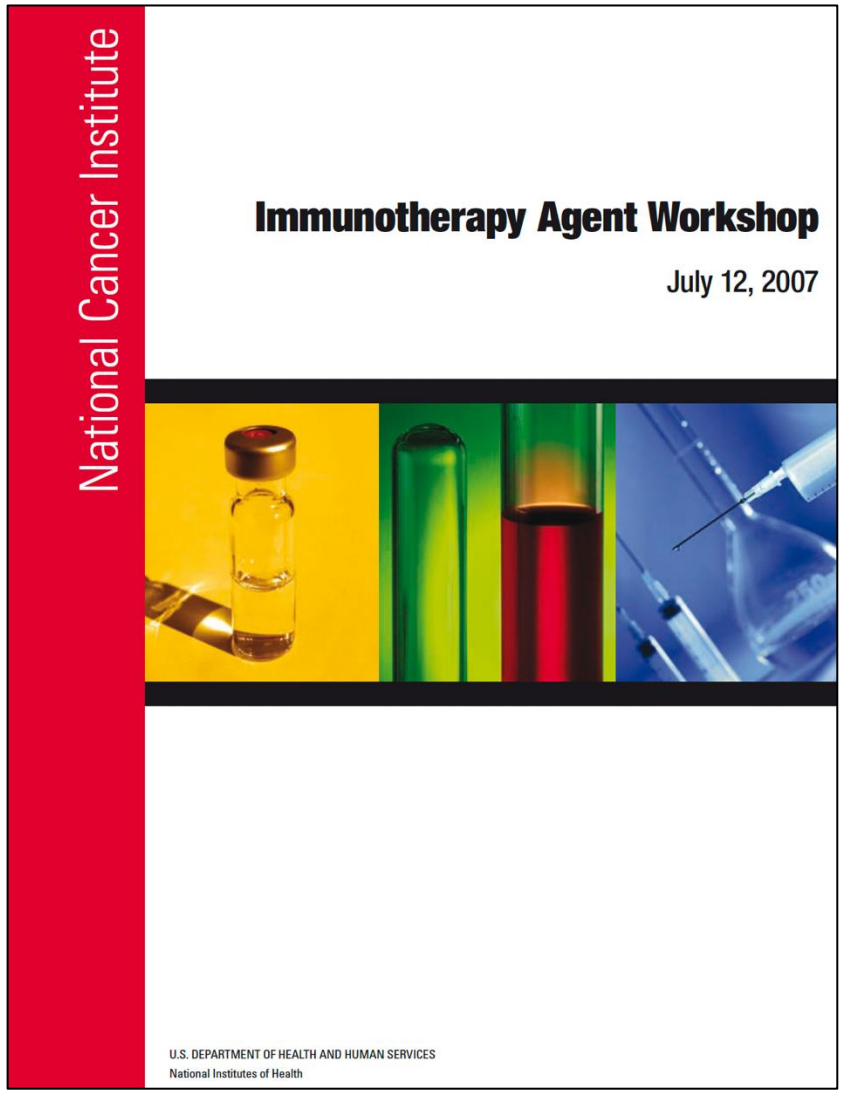


Table 1. Final Rankings of Agents with High Potential for Use in Treating Cancer

Rank*	Agent	Agent Category
1	IL-15	T-Cell Growth Factor
2	Anti-Programmed Death-1 (PD1)and/or anti–B7-H1 (PD1 Ligand)	**T-Cell Checkpoint Blockade Inhibitor
3	IL-12	Vaccine Adjuvant
4	Anti-CD40 and/or CD40L	Antigen Presenting Cell Stimulator
5	IL-7	T-Cell Growth Factor
6	CpG	Vaccine Adjuvant
7	1-Methyl Tryptophan	Enzyme Inhibitor
8	Anti-CD137 (anti–4-1BB)	T-Cell Stimulator
9	Anti–TGF-beta	Signaling Inhibitor
10	Anti–IL-10 Receptor or Anti–IL-10	Suppression Inhibitor

2008: IL-15 Ranked #1 "*Immunotherapy Drug that Could Cure Cancer*"

2008

Martin A. 'Mac' Cheever

Dr. Martin A. 'Mac' Cheever
1994 - 2021

Twelve immunotherapy drugs that could cure cancers

Table 2. Twelve immunotherapy drugs that could cure cancer

Agent category	Agent
T-cell growth factors	IL-15
	IL-7
T-cell checkpoint blockade inhibitor	Anti-PD1 and/or anti-B7-H1 (PD-1L)
Antigen-presenting cell stimulator	Anti-CD40 and/or CD40L
Enzyme inhibitor	1MT
T-cell stimulator	Anti-CD137 (anti-4-1BB)
DC growth factor/ vaccine adjuvant	Flt3L
Vaccine adjuvants	IL-12
	CpG
	MPL
	Poly I:C and/or PolyICLC
	Resiquimod and/or 852A

Eight agents on the NCI ranked list (*Table 1*) are excluded from this list, only as less is known about their effects on T-cell vaccine responses. The agents not included as well as many other might ultimately prove to have greater immunotherapy efficacy than the agents chosen for this review.

Table 1. Rankings of agents with high potential for use in treating cancer

Rank*	Agent	Agent category
1	IL-15	T-cell growth factor
2	Anti-PD1 and/or anti-B7-H1 (PD-1L)	*T-cell checkpoint blockade inhibitor
3	IL-12	Vaccine adjuvant
4	Anti-CD40 and/or CD40L	Antigen presenting cell stimulator
5	IL-7	T-cell growth factor
6	CpG	Vaccine adjuvant
7	1MT	Enzyme inhibitor
8	Anti-CD137 (anti-4-1BB)	T-cell stimulator
9	Anti-TGF-β	Signaling inhibitor
10	Anti-IL-10 Receptor or Anti-IL-10	Suppression inhibitor
11	Flt3L	Dendritic cell growth factor/ vaccine adjuvant
12	Anti-glucocorticoid-induced TNF receptor (GITR)	T-cell stimulator
13	CCL21 adenovirus	T-cell attracting chemokine
14	MPL	Vaccine adjuvant
15	Poly I:C and/or PolyICLC	Vaccine adjuvant
16	Anti-OX40	T-cell stimulator
17	Anti-B7-H4	T-cell checkpoint blockade inhibitor
18	Resiquimod and/or 852A	Vaccine adjuvant
19	LIGHT and/or LIGHT vector	T-cell stimulator
20	Anti-lymphocyte activation gene-3 (LAG-3)	T-cell checkpoint blockade inhibitor

*Anti-CTLA-4, a T-cell checkpoint blockade inhibitor, was considered of exceedingly high value but was not included on the list, as it is being produced by two companies and is likely to be approved by the FDA within the foreseeable future.

Lessons Learned After 55 Years of Cancer Drug Development as Standard of Care

- High dose chemoradiation induces lymphopenia
- Epogen to treat anemia (RBC) to enable more chemoradiation
- Neupogen (G-CSF) to treat neutropenia (ANC) to enable more chemoradiation
- IL-2 stimulates immunosuppressive T cells
- Leukine (GM-CSF) stimulates immunosuppressive neutrophils (N2's)

Hidden in Plain Sight

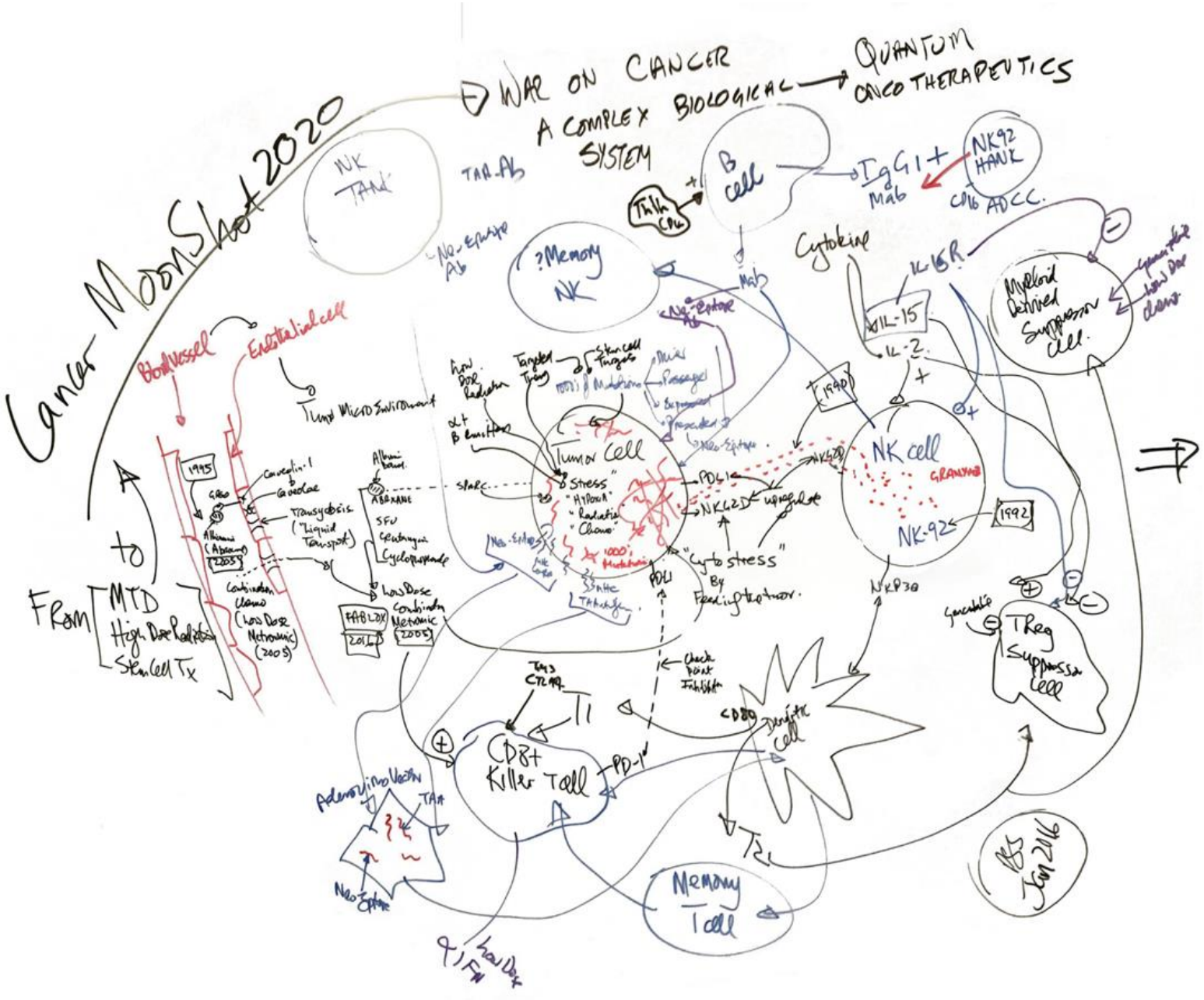
1. Lymphopenia Significantly Reduces Survival Across All Tumor Types
2. Lymphopenia Reduces Survival in General US Population
3. Absolute Lymphocyte Count (ALC) Ignored
4. IL-15 Ranked #1 Cytokine to Cure Cancer
5. IL-15 Reverses Lymphopenia

The Pursuit of the Cancer Vaccine

Hidden in Plain Sight

1. Lymphopenia Significantly Reduces Survival Across All Tumor Types
2. Lymphopenia Reduces Survival in General US Population
3. Absolute Lymphocyte Count (ALC) Ignored
4. IL-15 Ranked #1 Cytokine to Cure Cancer
5. IL-15 Reverses Lymphopenia

Winning the War Against Cancer: Harnessing the Power Within



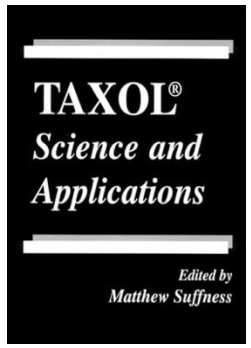
“The Cancer Vaccine”

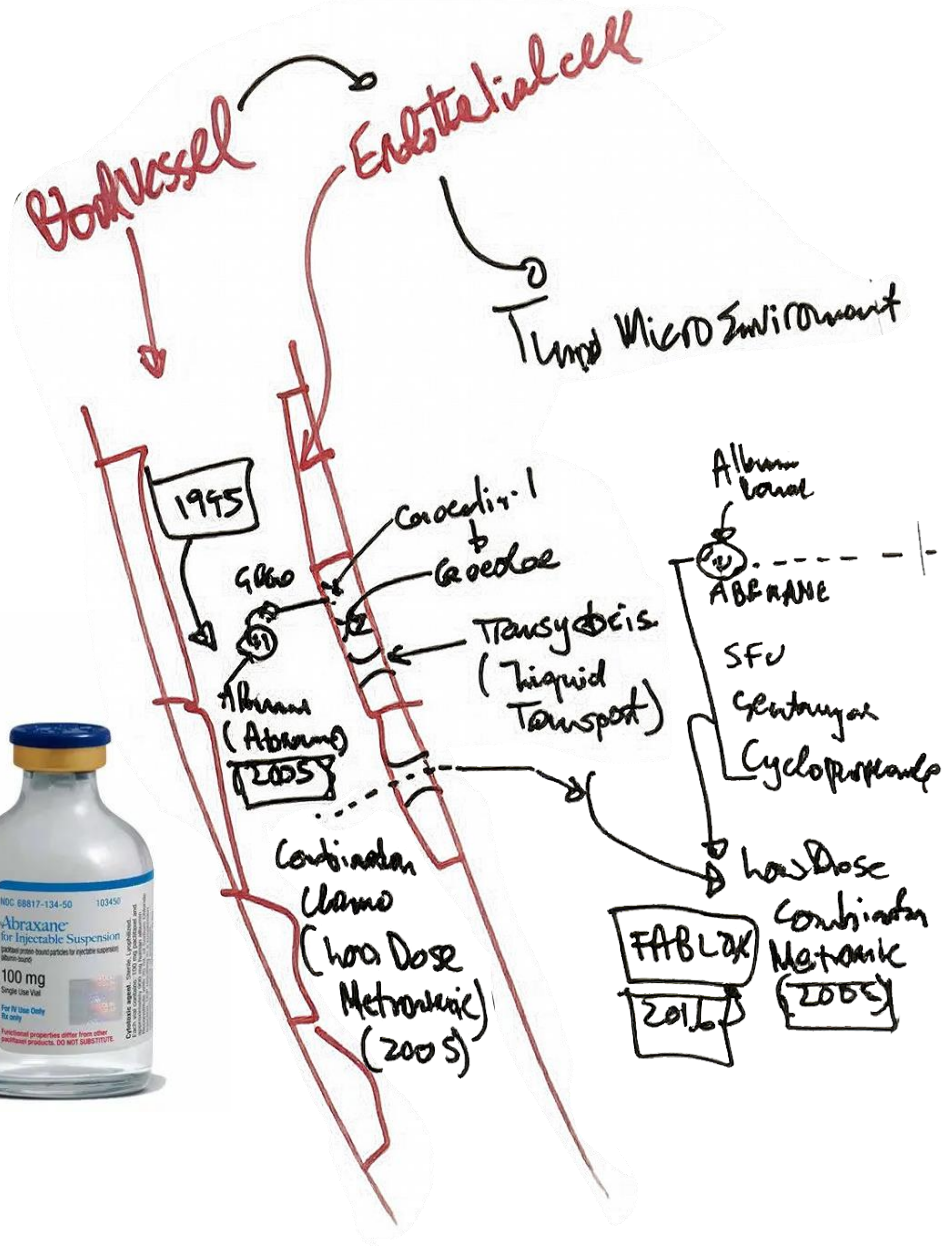
Hypothesis:
Orchestrating the innate and adaptive immune system drives immunogenic cell death with durable complete remission of cancer independent of tumor type

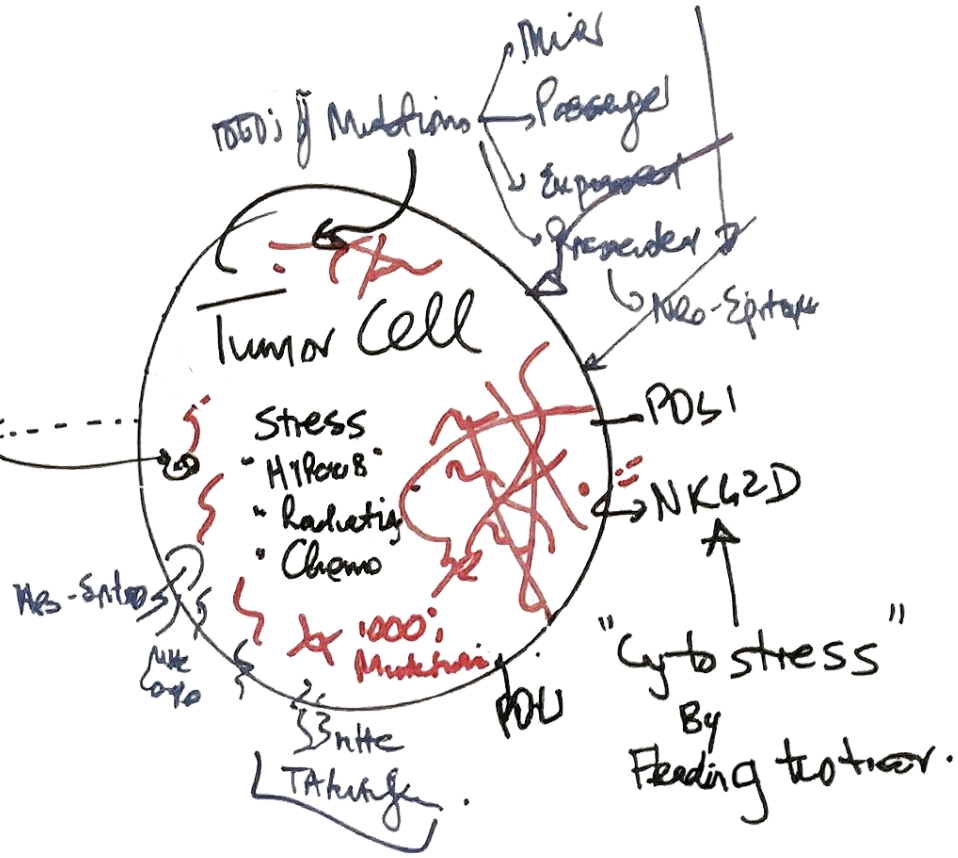
Presented to FDA, Oncology Center of Excellence (OCE) 2016

PSS Mind Map Jan 2016

Step 1: 2005 - Entering the Tumor Microenvironment



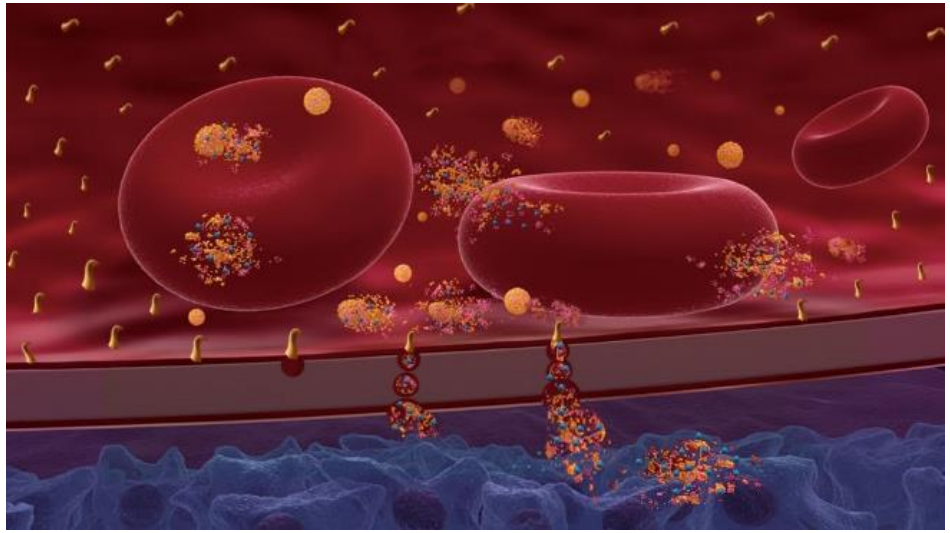




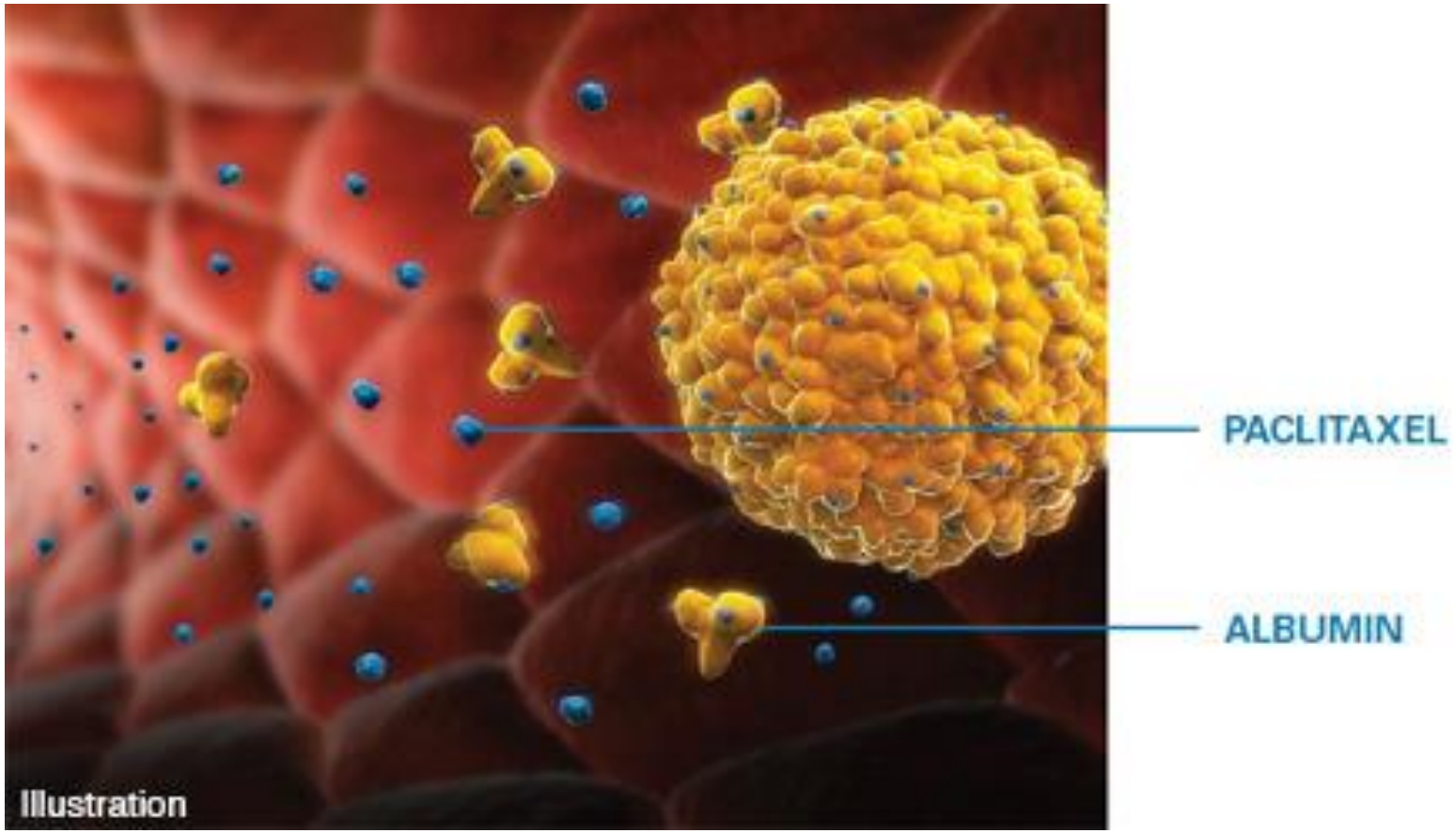
Low-Dose Metronomic Chemo Induction of DAMPS (Damage Associated Molecular Patterns)

Quest to Penetrate the Tumor Microenvironment

Abraxane



Albumin Nanoparticle of Paclitaxel
To Penetrate the Blood Vessel Wall



2017: M1 to M2 Macrophages in Pancreatic Cancer

Modulation of the Tumor Microenvironment with Chemotherapy

Cancer Immunology Miniatures

Cancer Immunology Research

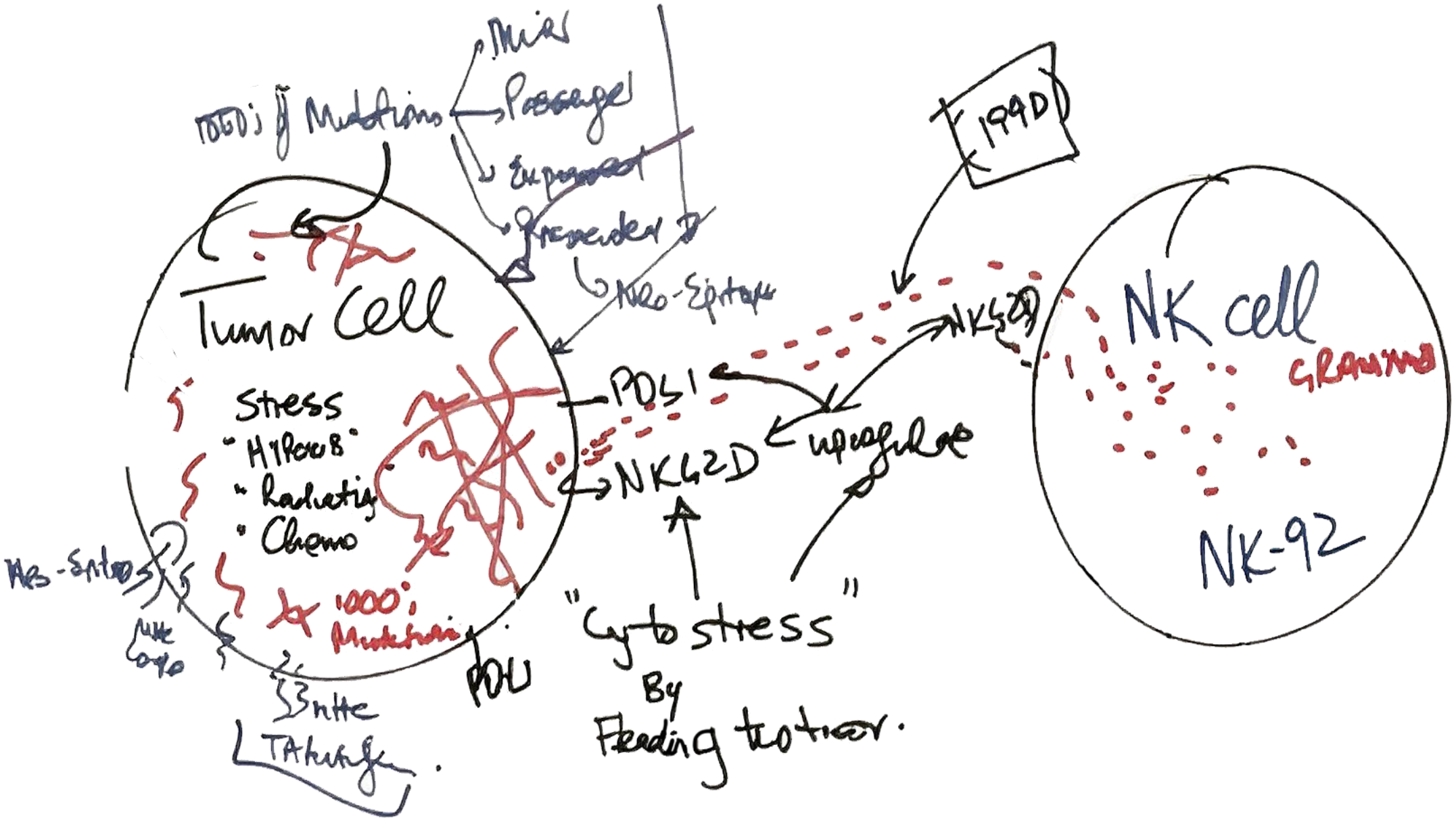
Macropinocytosis of Nab-paclitaxel Drives Macrophage Activation in Pancreatic Cancer

Jane Cullis[1], Despina Siolas[1], Antonina Avanzi[1], Sugata Barui[2], Anirban Maitra[2], and Dafna Bar-Sagi[1]

Abstract

Pancreatic cancer is a devastating disease that is largely refractory to currently available treatment strategies. Therapeutic resistance is partially attributed to the dense stromal reaction of pancreatic ductal adenocarcinoma tumors that includes a pervasive infiltration of immunosuppressive (M2) macrophages. Nab-paclitaxel (trade name Abraxane) is a nanoparticle albumin-bound formulation of paclitaxel that, in combination with gemcitabine, is currently the first-line treatment for pancreatic cancer. Here, we show that macrophages internalized nab-paclitaxel via macropinocytosis. The macropinocytic uptake of nab-paclitaxel induced macrophage immunostimulatory (M1) cytokine expression and synergized with IFNγ to promote inducible nitric oxide synthase expression in a TLR4-dependent manner. Nab-paclitaxel was internalized by tumor-associated macrophages *in vivo*, and therapeutic doses of nab-paclitaxel alone, and in combination with gemcitabine, increased the $MHCII^{+}CD80^{+}CD86^{+}$ M1 macrophage population. These data revealed an unanticipated role for nab-paclitaxel in macrophage activation and rationalized its potential use to target immune evasion in pancreatic cancer. *Cancer Immunol Res; 5(3); 182–90.* ©2017 AACR.

Step 2: 1990 - The Natural Killer Cell



1990: Recognition of the Power of Natural Killer Cells

1990

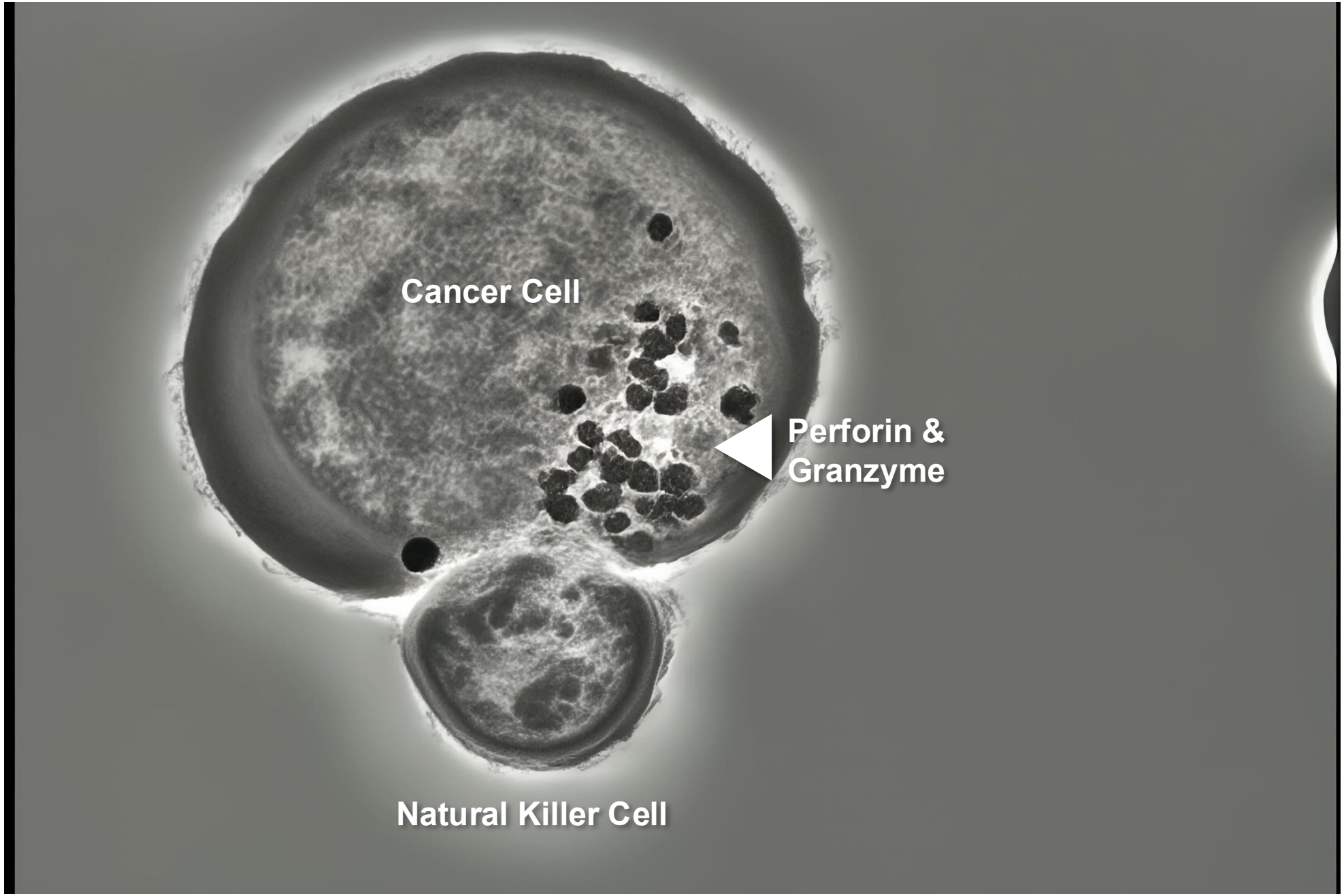
> Horm Metab Res Suppl. 1990:25:215-9.

Prevention of CTL and NK cell-mediated cytotoxicity by microencapsulation

P Soon-Shiong [1], Z N Lu, I Grewal, R Lanza, W Clark

Affiliations + expand

PMID: 2088973

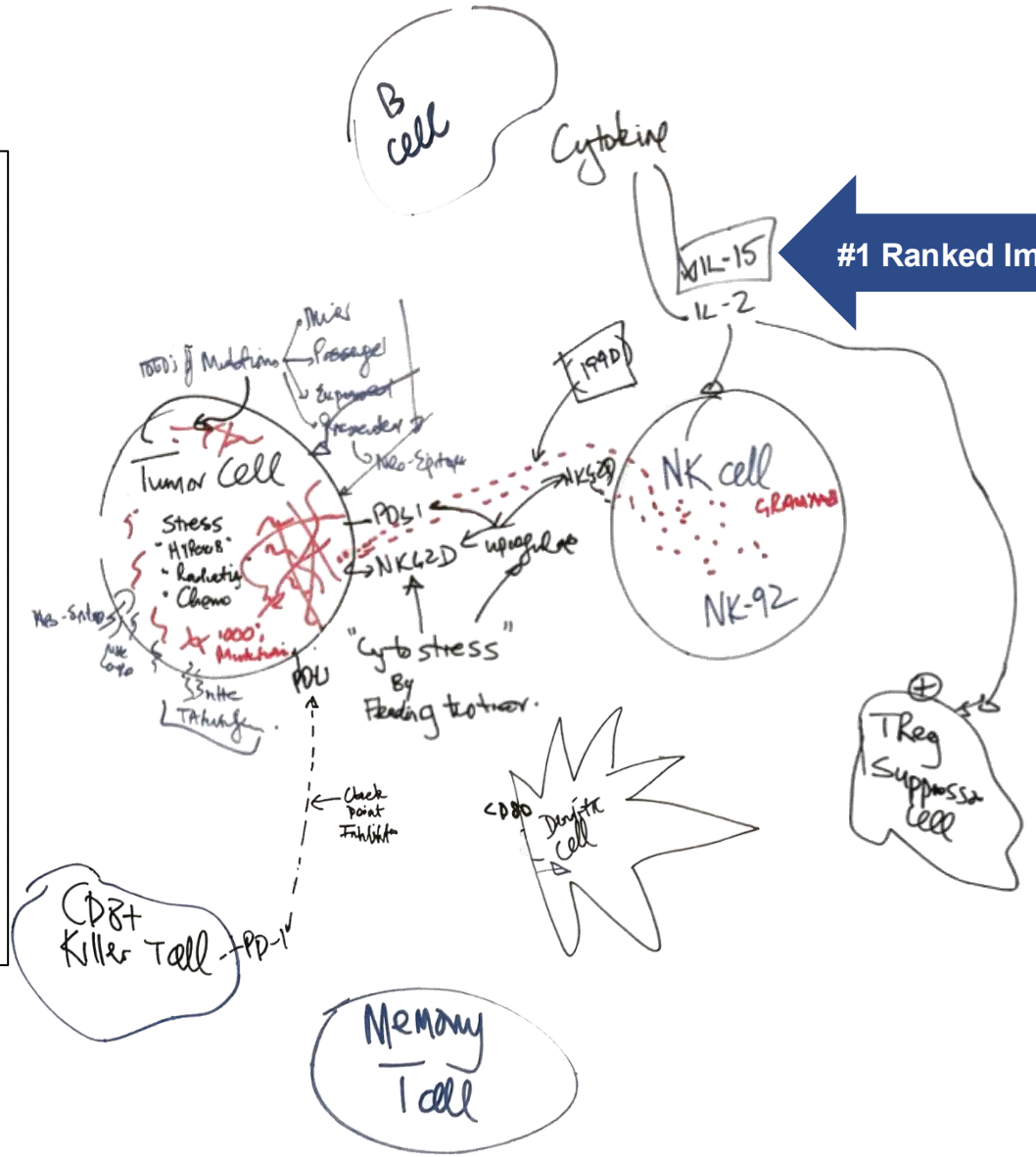

Cancer Cell
Perforin &
Granzyme
Natural Killer Cell

Step 3: 2016 – Harnessing The Power of IL-15

Table 2. Twelve immunotherapy drugs that could cure cancer

Agent category	Agent
T-cell growth factors	IL-15
	IL-7
T-cell checkpoint blockade inhibitor	Anti-PD1 and/or anti-B7-H1 (PD-1L)
Antigen-presenting cell stimulator	Anti-CD40 and/or CD40L
Enzyme inhibitor	1MT
T-cell stimulator	Anti-CD137 (anti-4-1BB)
DC growth factor/ vaccine adjuvant	Flt3L
Vaccine adjuvants	IL-12
	CpG
	MPL
	PolyI:C and/or PolyICLC
	Resiquimod and/or 852A

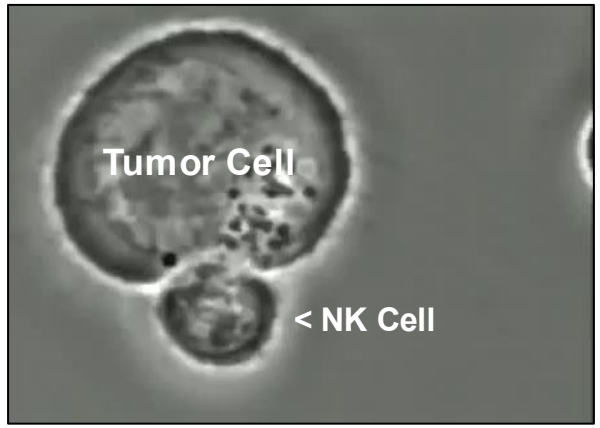
Eight agents on the NCI ranked list (*Table 1*) are excluded from this list, only as less is known about their effects on T-cell vaccine responses. The agents not included as well as many other might ultimately prove to have greater immunotherapy efficacy than the agents chosen for this review.



#1 Ranked Immunotherapy to Curing Cancer

IL-15 Agonist

Harnessing the Power of the Body's Immune System to Cure Cancer: IL-15 Ranked #1



Approved 2024

2022: Healthy Volunteers with ANKTIVA (IL-15 Superagonist)

The Journal of Immunology

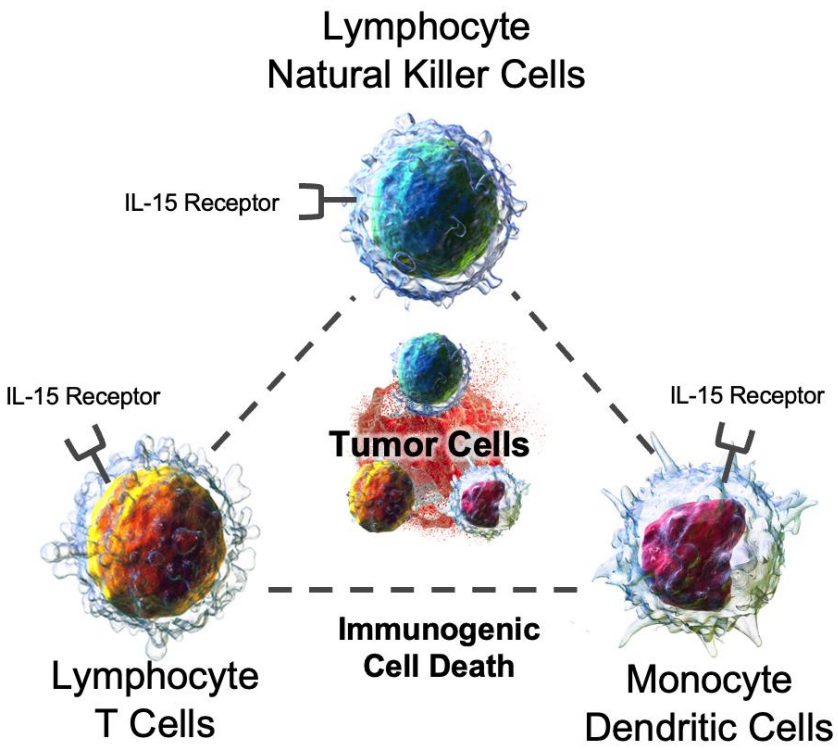
2022

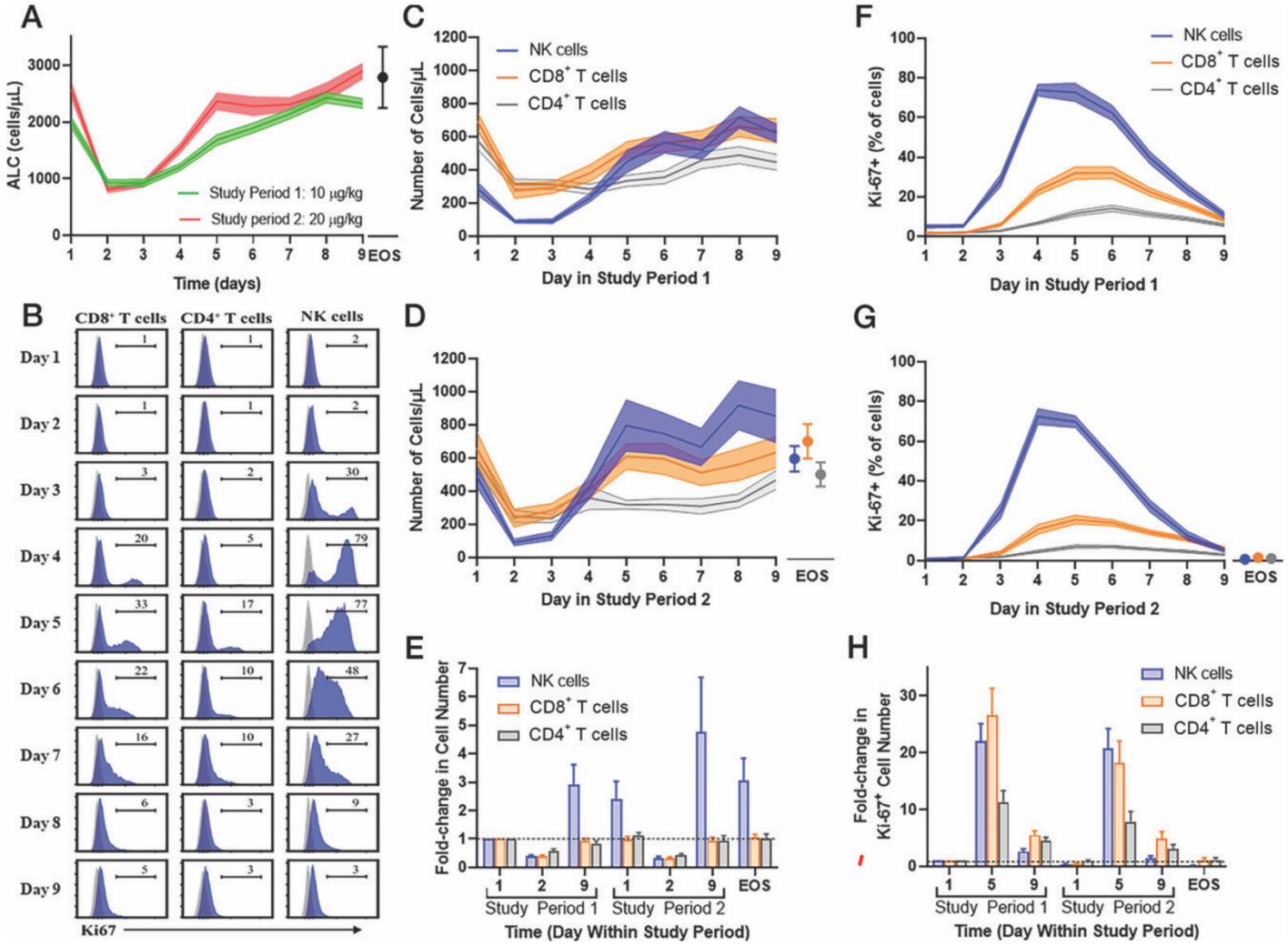
RESEARCH ARTICLE | MARCH 15 2022

Phase I Trial Characterizing the Pharmacokinetic Profile of N-803, a Chimeric IL-15 Superagonist, in Healthy Volunteers FREE

Mark P. Rubinstein; ... et. al

J Immunol (2022) 208 (6): 1362–1370.
https://doi.org/10.4049/jimmunol.2100066





2023: IL-15 Producing Cells and IL-15 Effects
A Decade of Collaboration with NCI

cells 2023 MDPI

Review

Exploiting an Interleukin-15 Heterodimeric Agonist (N803) for Effective Immunotherapy of Solid Malignancies

Grace Lui [1], Christine M. Minnar [1], Patrick Soon-Shiong [2], Jeffrey Schlom [1,*,†] and Sofia R. Gameiro [1,†]

[1] Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA; grace.lui@nih.gov (G.L.); christine.minnar@nih.gov (C.M.M.); sofia.gameiro@nih.gov (S.R.G.)
[2] ImmunityBio, Culver City, CA 90232, USA; pss@nantworks.com
* Correspondence: schlomj@mail.nih.gov
† These authors contributed equally to this work.

6. Discussion

The pleiotropic and unique biology of IL-15 render this cytokine very attractive for the agnostic treatment of cancer. Given the safety challenges of recombinant IL-15, the pioneering development of N803 has enabled safe administration to patients and the clinical evaluation of the unrealized potential of IL-15 as a cancer therapeutic [24,59,60]. Furthermore, preclinical and clinical studies have demonstrated that N803 induces tumor control while overcoming the short half-life of recombinant IL-15 [24,61,69]. Importantly, both intravenous and subcutaneous N803 administration have demonstrated an improved safety profile relative to rIL-15, including no reported dose-limiting toxicities [29,31]. Intravenous delivery allows for systemic and broad cytokine distribution to off-target sites and can result in high cytokine levels, collectively amenable to the development of immune-related AEs. In contrast, subcutaneous delivery may enable lymphatic distribution conducive to the targeted delivery to lymph nodes upstream of tumor lesions, where the most effective dendritic cell priming of T cells may occur. While N803 was shown to be safely administered to

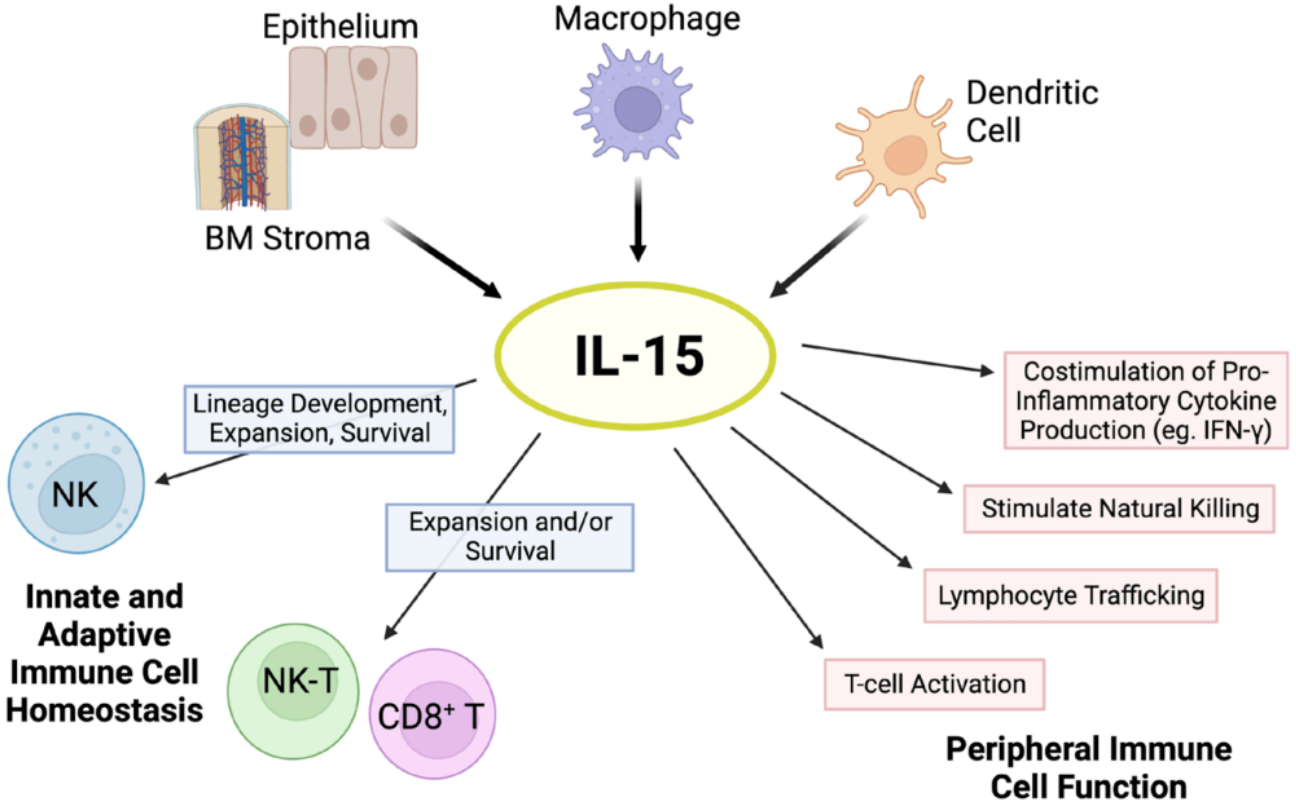


Figure 1. Pleiotropic effects of IL-15. The cytokine IL-15 is produced by multiple cell types, such as activated dendritic cells, monocytes/macrophages, epithelial cells, and bone marrow (BM) stromal cells. IL-15 is critical for natural killer (NK) cell lineage development, survival, and proliferation. This cytokine holds important modulatory effects in the expansion and survival of CD8+ T cells, including memory formation, and lymphocyte cytotoxic function. In addition, IL-15 has pleiotropic effects on peripheral innate and adaptive immunity.

April 2024: ANKTIVA – An IL-15 Superagonist Activating and Proliferating IL-15 Positive Lymphocytes

ANKTIVA USA Package Insert, Approved April 2024

IL-15 Superagonist

12.1 Mechanism of Action

Nogapendekin alfa inbakicept-pmln is an IL-15 receptor agonist. IL-15 signals through a heterotrimeric receptor that is composed of the common gamma chain (γc) subunit, the beta chain (βc) subunit, and the IL-15-specific alpha subunit, IL-15 receptor α. IL-15 is *trans*-presented by the IL-15 receptor α to the shared IL-2/IL-15 receptor (βc and γc) on the surface of $CD4^+$ and $CD8^+$ T cells and NK cells.

Binding of nogapendekin alfa inbakicept-pmln to its receptor results in proliferation and activation of NK, $CD8^+$, and memory T cells without proliferation of immuno-suppressive Treg cells. In vivo, intravesicular nogapendekin alfa inbakicept-pmln alone or in combination with BCG showed anti-tumor activity when compared to BCG alone, in a carcinogen-induced model of bladder cancer in immunocompetent rats.

"binding of NAI to its receptor [IL-15] results in proliferation and activation of [IL-15+ lymphocytes] NK, CD8+, and Memory T cells without proliferation of immuno-suppressive Treg cells…

2007: Seminal Workshop by NCI, NIH, FDA to Rank Immunotherapy Molecules with the Potential to Cure Cancer

Ranked #1

Twenty Years in the Making

Approved in Bladder (33 Countries) and Lung Cancer (Saudi, SFDA)

Ranked #2

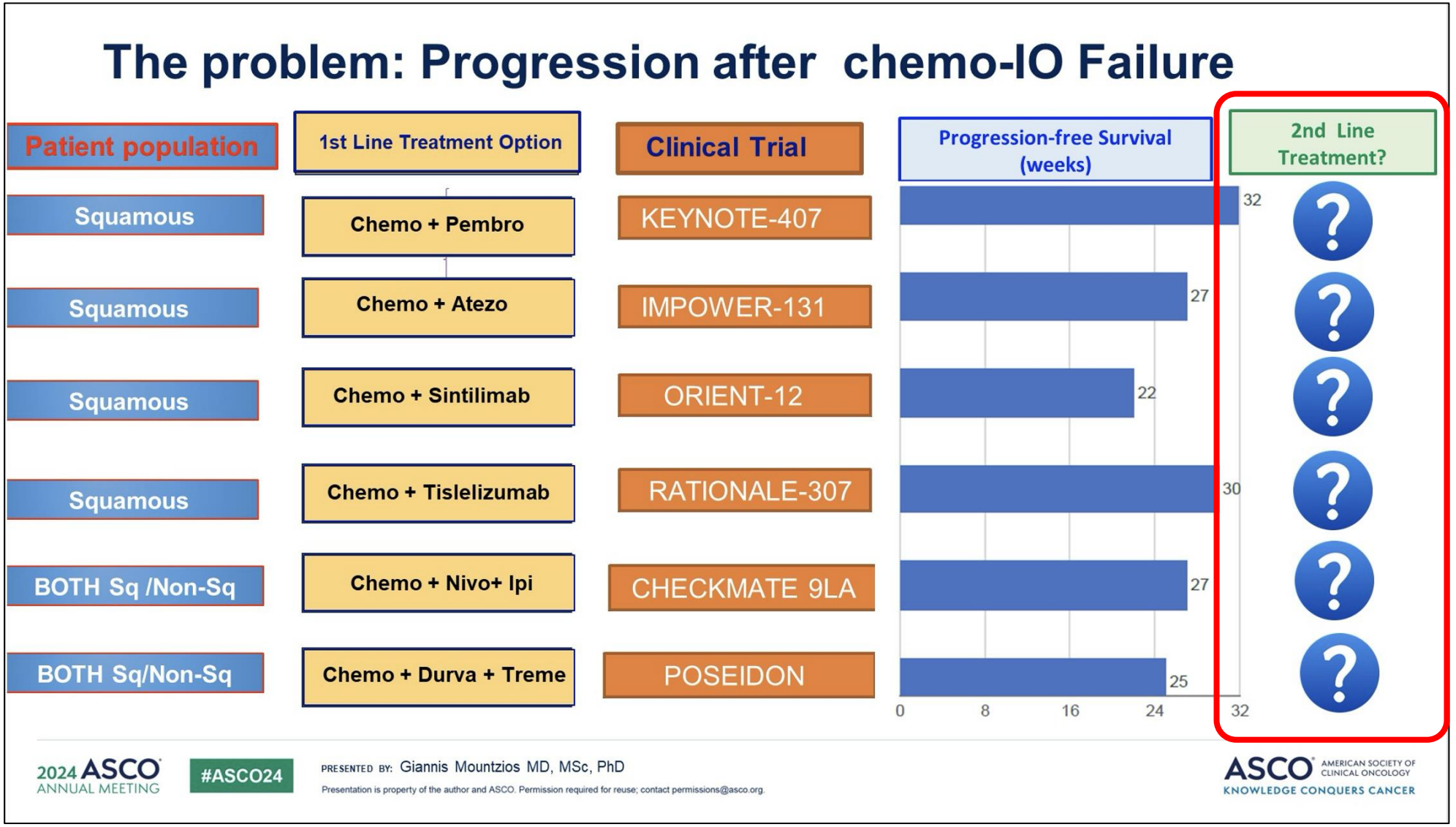
40+ Approvals by 2025
Many Single-Arm Trials
Micro-Satellite Stable Across Multiple Tumor Types

Table 1. Final Rankings of Agents with High Potential for Use in Treating Cancer

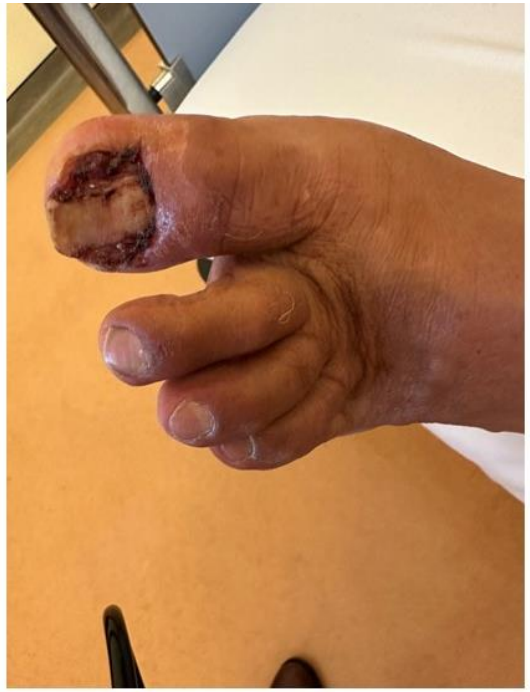
Rank*	Agent	Agent Category
1	IL-15	T-Cell Growth Factor
2	Anti-Programmed Death-1 (PD1)and/or anti–B7-H1 (PD1 Ligand)	**T-Cell Checkpoint Blockade Inhibitor
3	IL-12	Vaccine Adjuvant
4	Anti-CD40 and/or CD40L	Antigen Presenting Cell Stimulator
5	IL-7	T-Cell Growth Factor
6	CpG	Vaccine Adjuvant
7	1-Methyl Tryptophan	Enzyme Inhibitor
8	Anti-CD137 (anti–4-1BB)	T-Cell Stimulator
9	Anti–TGF-beta	Signaling Inhibitor
10	Anti–IL-10 Receptor or Anti–IL-10	Suppression Inhibitor
11	Flt3L	Dendritic Cell Growth Factor/ Vaccine Adjuvant
12	Anti-Glucocorticoid-Induced TNF Receptor (GITR)	T-cell Stimulator
13	CCL21 Adenovirus	T-Cell Attracting Chemokine
14	Monophosphoryl Lipid A (MPL)	Vaccine Adjuvant
15	Poly I:C and/or Poly ICLC	Vaccine Adjuvant
16	Anti-OX40	T-Cell Stimulator
17	Anti–B7-H4	T-Cell Checkpoint Blockade Inhibitor
18	Resiquimod and/or 852A	Vaccine Adjuvant
19	LIGHT and/or LIGHT vector	T-Cell Stimulator
20	Anti–Lymphocyte Activation Gene-3 (LAG-3)	T-Cell Checkpoint Blockade Inhibitor

2024 Challenges Facing Immunotherapy

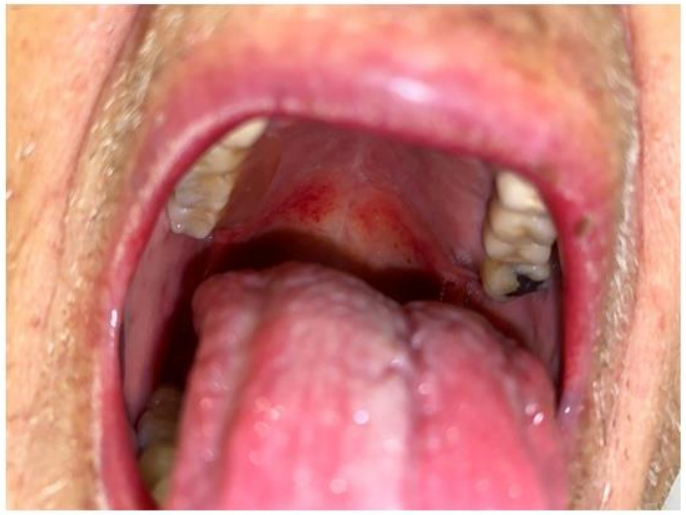
2024: The Problem Facing Oncologists Checkpoint Inhibitor Failures



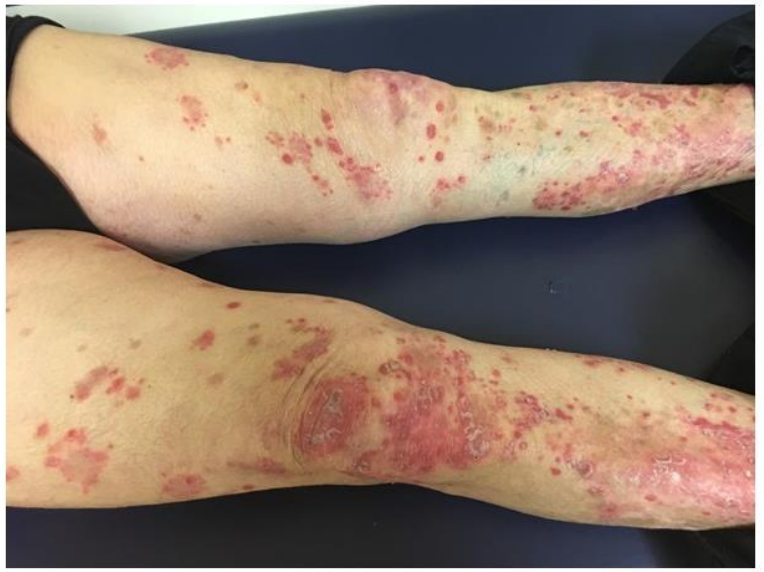
Why Patients (and Oncologists) Do Not Like Docetaxel



Paronychia Grade 3



Stomatitis Grade 2



Erythematopapular Rash Grade 3

All patient characteristics de-identified. All Patients provided written Informed consent for anonymized publication

PRESENTED BY: Giannis Mountzios MD, MSc, PhD

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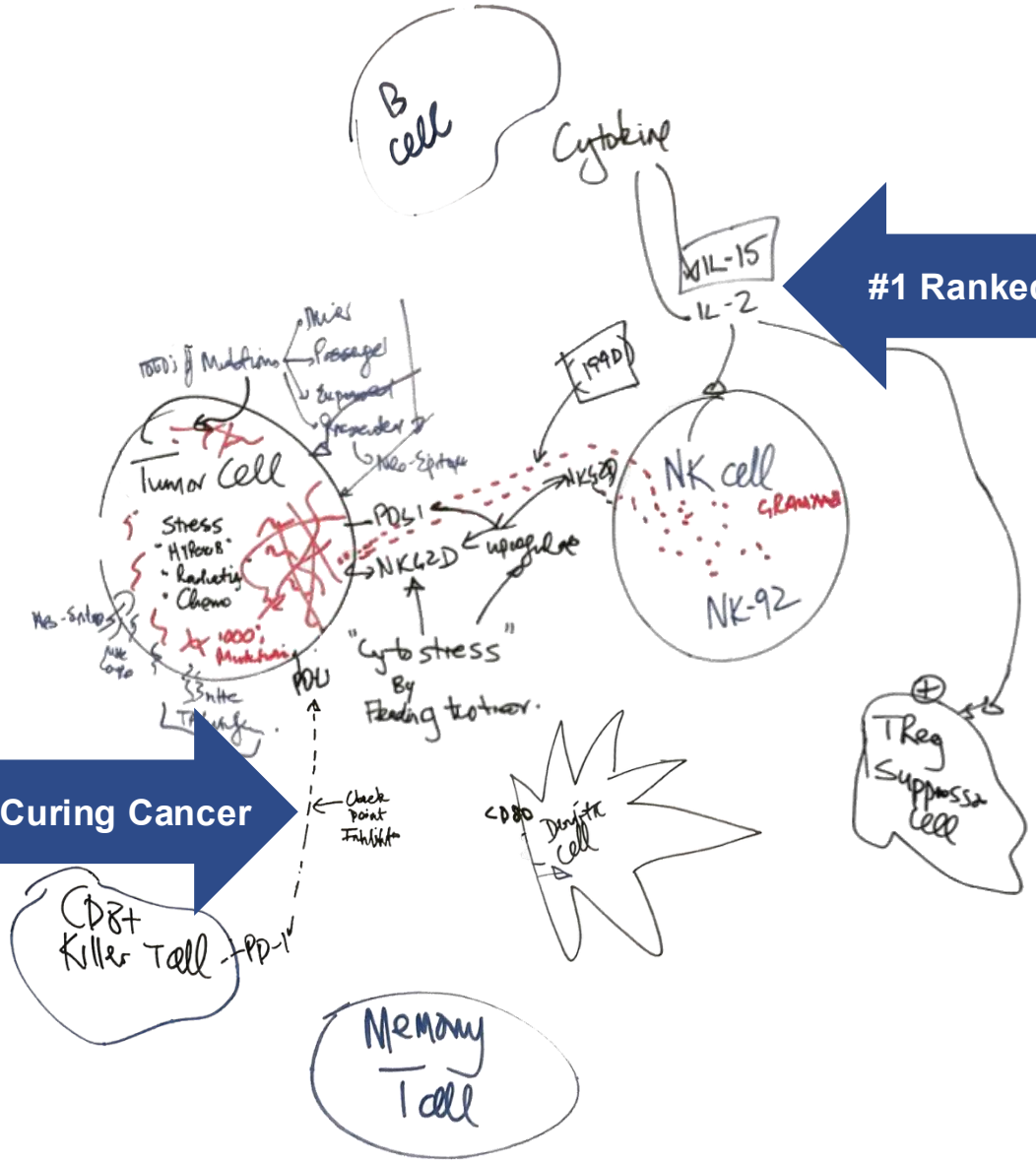
Photo Courtesy Dr Giannis Mountzios

Step 4: 2025 Combination of IL-15 with Checkpoint Inhibitors



#1 Ranked Immunotherapy to Curing Cancer

IL-15 Agonist

#2 Ranked Immunotherapy to Curing Cancer

Checkpoint Inhibitor

Randomized Clinical Trial: ANKTIVA + CPI versus CPI Alone

Sustained Mean ALC Increase and Percentage Change with ANKTIVA Over 27 Weeks

Mean ALC Values (Lymphocytes/uL)	Experimental CPI + ANKTIVA (Lymphocytes/uL)	Control CPI Alone (Lymphocytes/uL)
Mean Baseline Absolute Lymphocyte Count (ALC)	**1,786**	**1,640**
Week 3	2,036	1,562
Week 6	2,391	1,540
Week 9	2,216	1,655
Week 12	2,283	1,566
Week 15	2,291	1,616
Week 18	2,217	1,536
Week 21	2,257	1,539
Week 24	2,104	1,469
Week 27	2,190	1,428
Significant Difference in ALC Over 27 Weeks Between ANKTIVA+CPI versus CPI Alone	P-value for Comparison of ALC Over Time Between Experimental & Control Arms Through 27 Weeks **P=0.0065**	

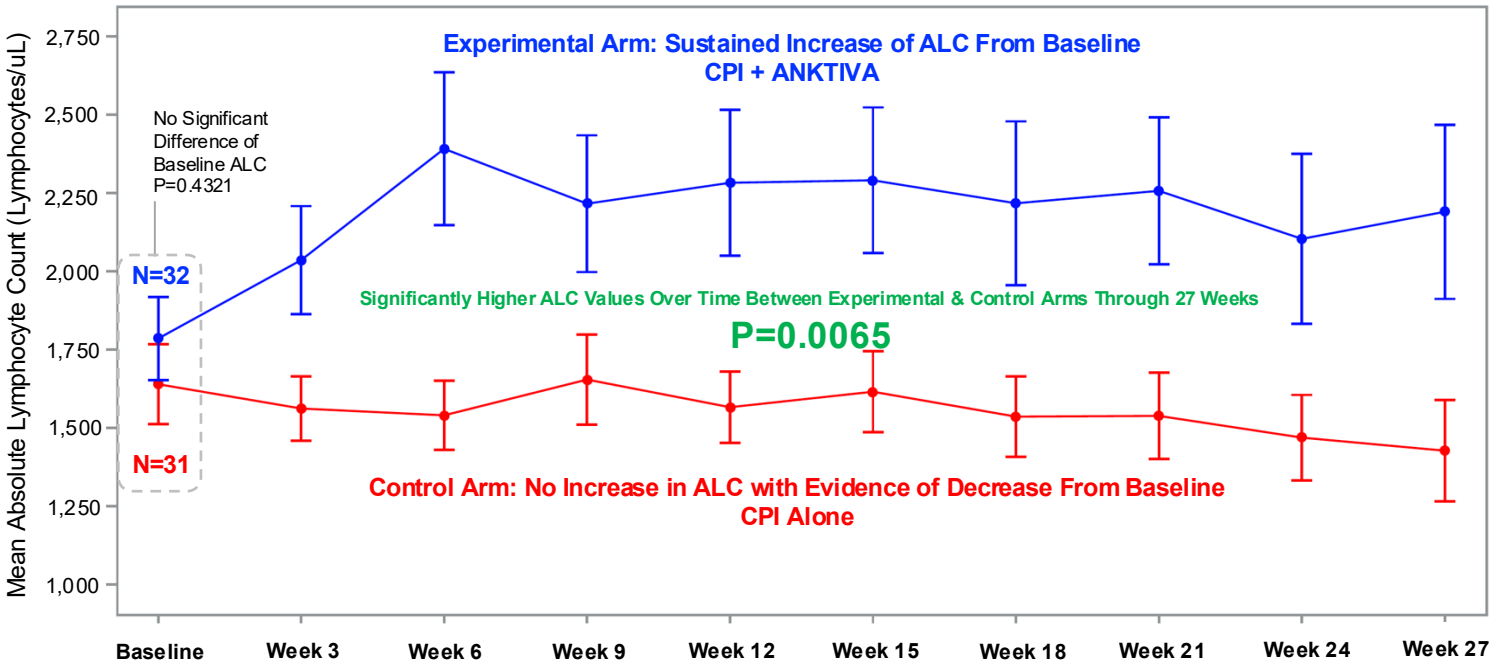
ALC Levels

Sustained Increase in ALC Over 27 Weeks

QUILT-2.023

- **<u>Significant</u> Difference in ALC Over Time Comparing the Two Arms in this Randomized Clinical Trial of First Line NSCLC Subjects (P=0.0065)**
- **<u>Sustained</u> Mean ALC Increase and Percentage Change with ANKTIVA Over 27 Weeks**

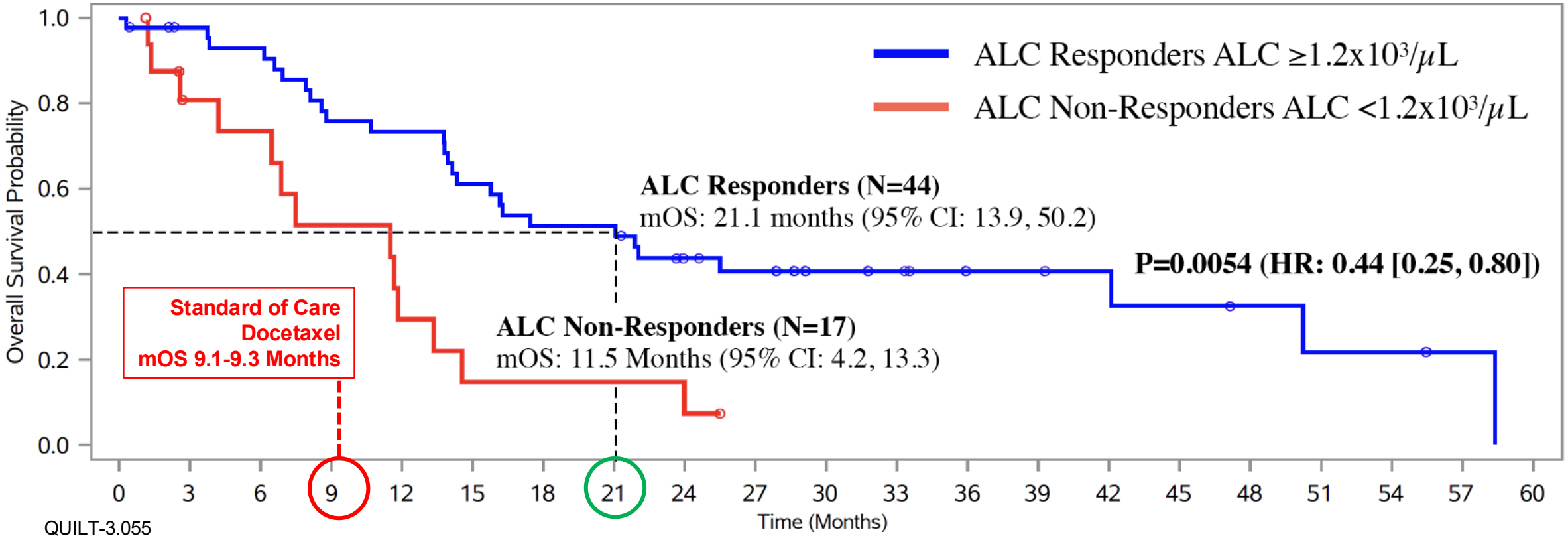
Randomized Control Study Demonstrates Significant Difference (P=0.0065) in ALC Increase Over Time with ANKTIVA + CPI versus CPI Alone



Significantly higher (P=0.0065) ALC values over time with ANKTIVA+CPI compared to CPI alone over 27 weeks, with sustained maintenance of ALC over baseline with ANKTIVA+CPI vs CPI Alone

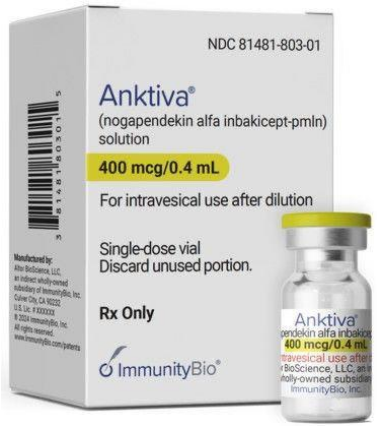
Single Arm Trial in 2L+ NSCLC Patients Progressing on Keytruda

Increased ALC Results in **21.1 Months** Overall Survival with ANKTIVA + Keytruda with ALC ≥1,200

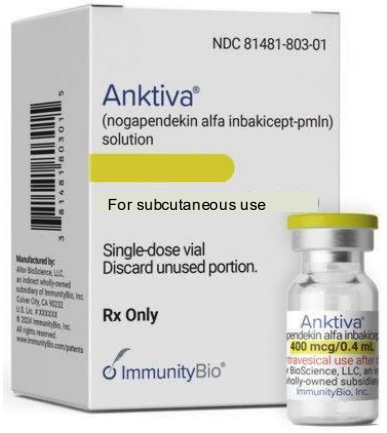


Patients achieving higher immune competence (ALC ≥1.2 ×10³ cells/μL) demonstrated additional survival benefit, with median OS of 21.1 months (HR 0.33; p=0.0009), independent of PD-L1 status, exceeding historical overall survival of 7-9 months with standard of care chemotherapy – ASCO 2025

Jan 2026: First Regulatory Authority to Approve ANKTIVA for Bladder and Lung Cancer



BLADDER CANCER
Based on QUILT-3.032



LUNG CANCER
Based on QUILT-3.055

Dr. Patrick Soon-Shiong
Executive Chairman
ImmunityBio

H.E. Dr. Hisham Saad Aljadhey
Chief Executive Officer
Saudi Food and Drug Authority (SFDA)

Kingdom of Saudi Arabia
Saudi Food & Drug Authority

Where Do We Go From Here? Harnessing the Power Within

Clinical Studies Addressing the Hypothesis for a Therapeutic & Preventative Cancer Vaccine

Therapeutic Cancer Vaccine

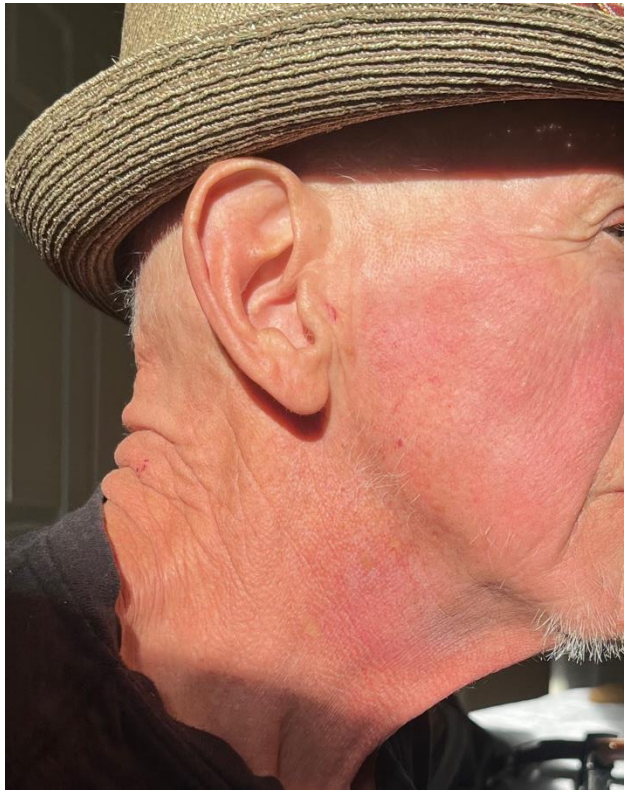
2016 to 2026

HPV+ Positive Head & Neck Cancer: ALC Increase Linked to HPV Viral Clearance and Complete Response

June 5, 2025

ALC: 1,320
HPV: 58

August 28, 2025



ALC Increase: 2,320
HPV Decrease: 19

November 2025

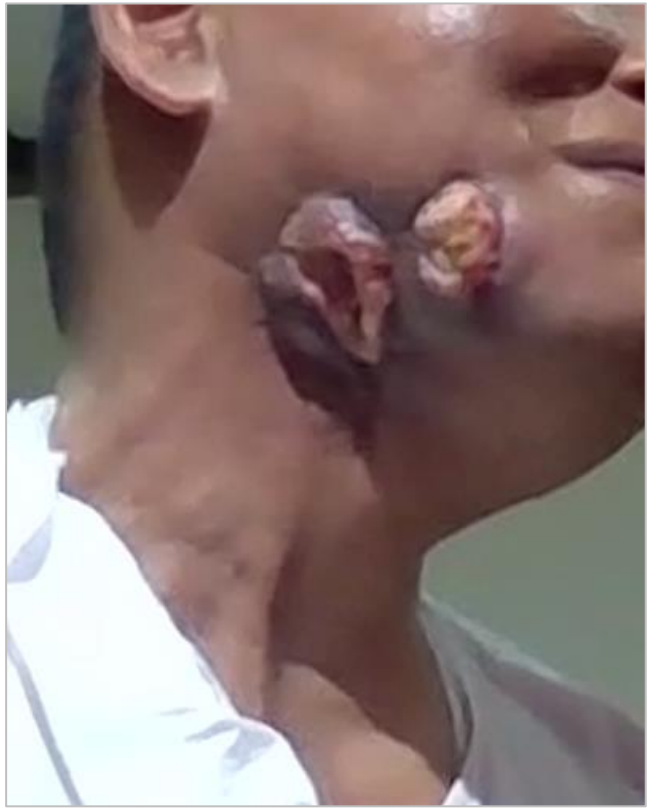
PET Scan
CT Scan
HPV: Normal
Complete Response

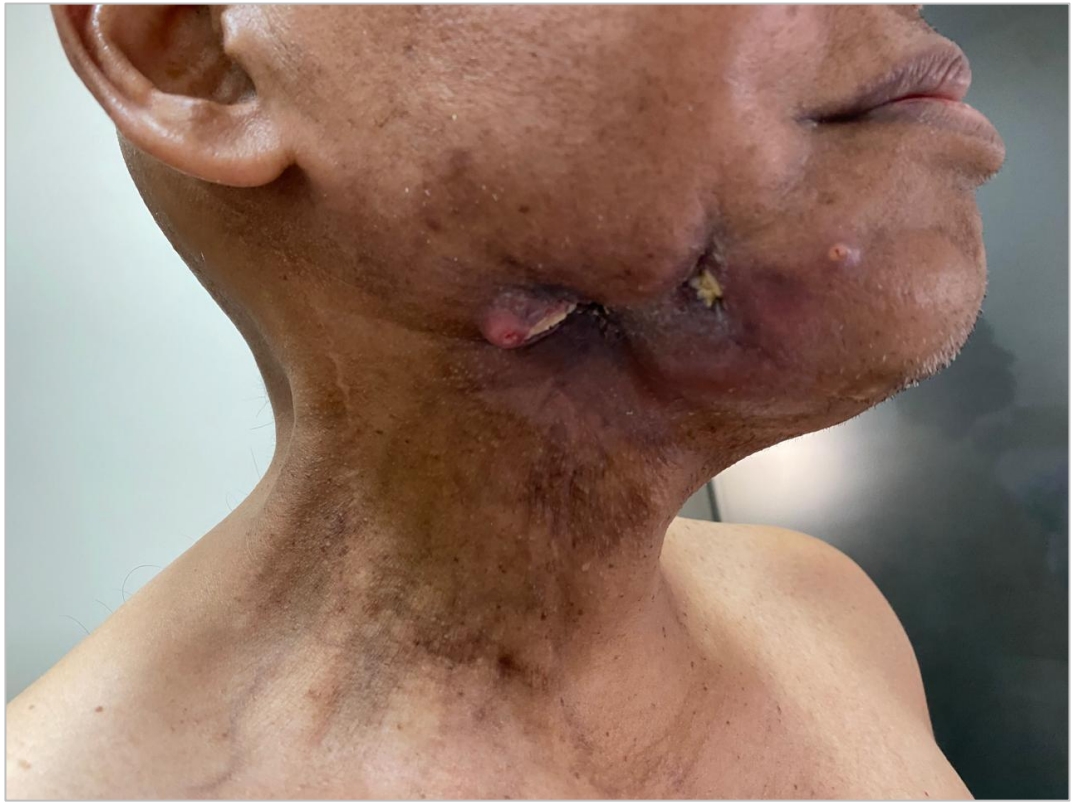
HPV- Negative Head & Neck Cancer: ALC Increase Linked to Rapid Response

Before
August 26, 2025

14 Days

After
September 9, 2025

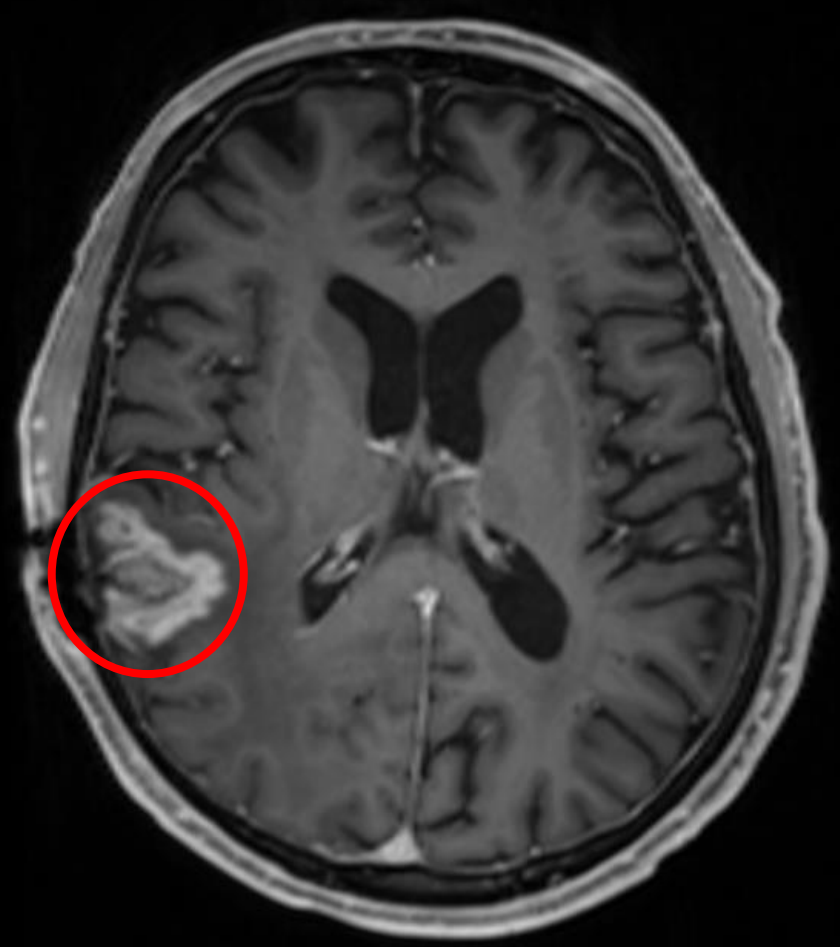


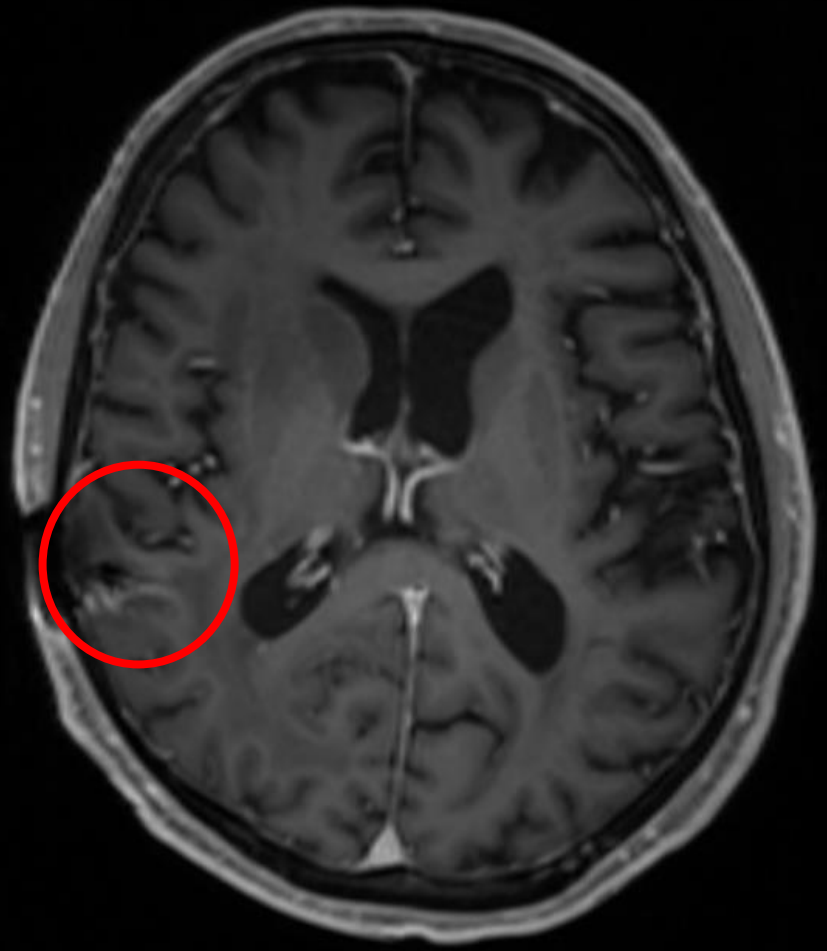


ALC: 460
HPV Negative

ALC Increase: 1,560
HPV Negative

Recurrent Glioblastoma Increase ALC with Near Complete Response

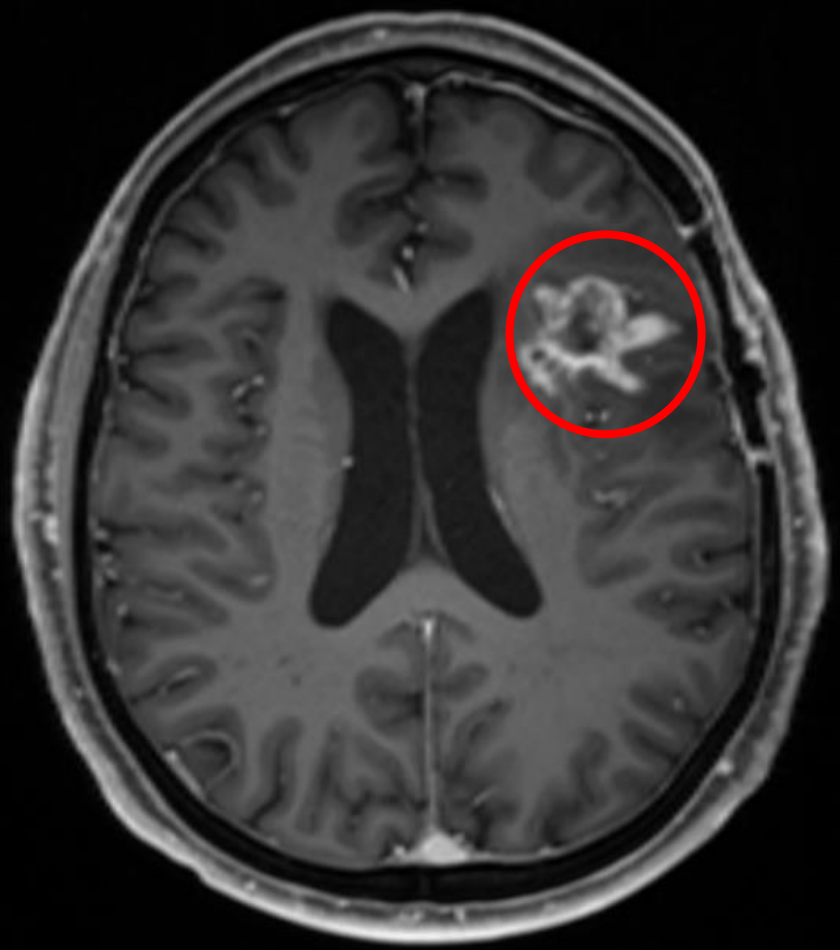


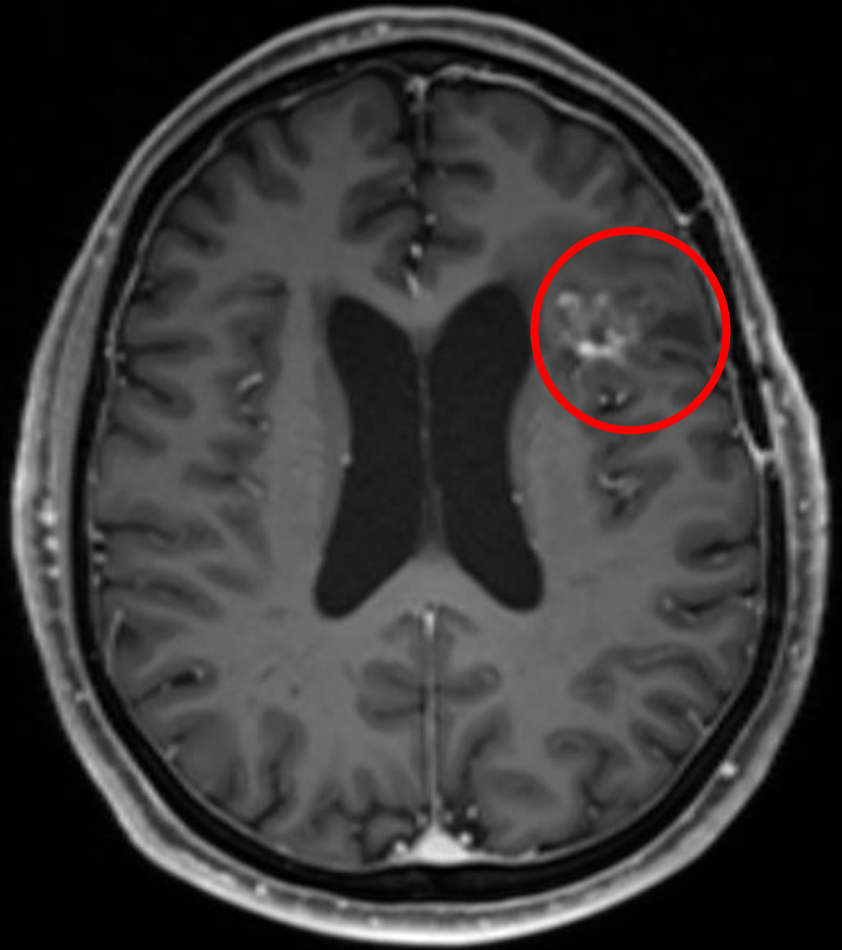


March 3, 2025
ALC: 500

October 15, 2025
Increased ALC: 1,100 ⬆

Recurrent Glioblastoma Increase ALC with Near Complete Response

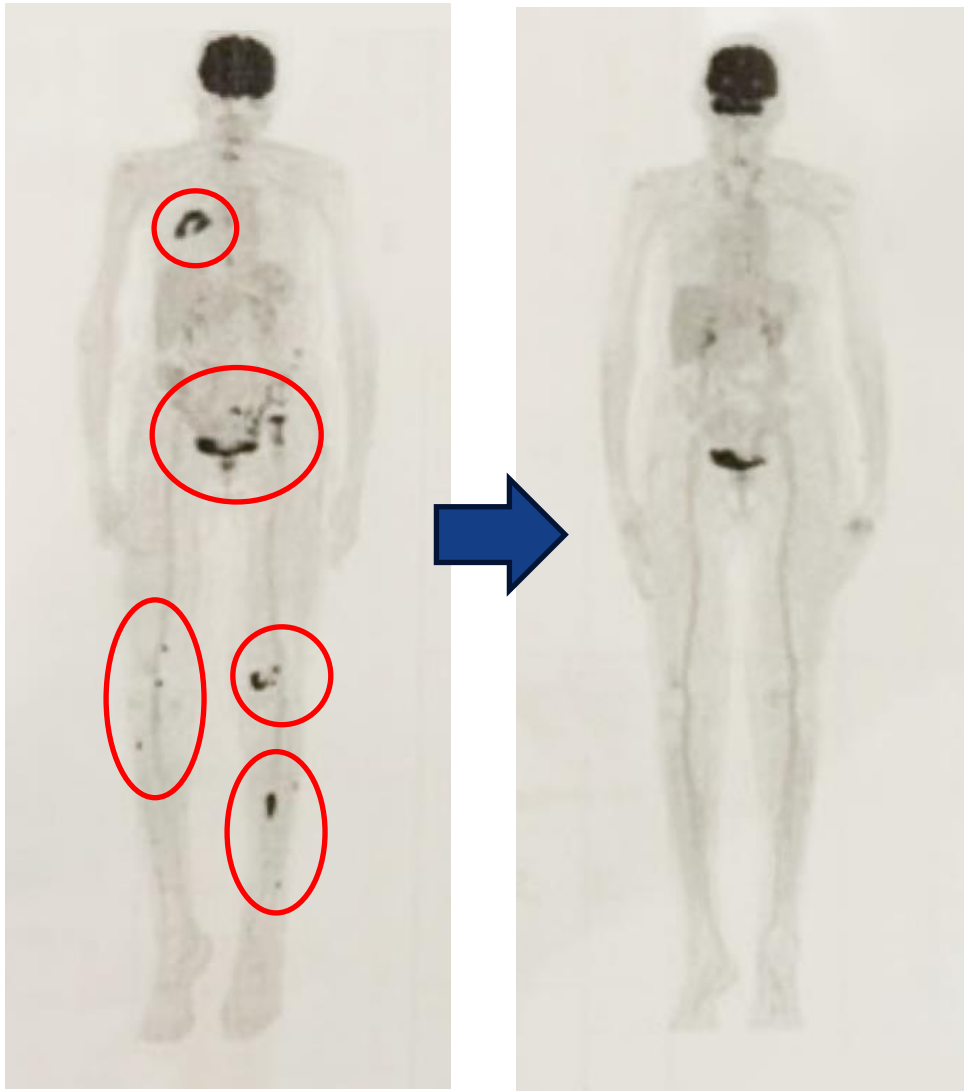




May 14, 2025
ALC: 1,100

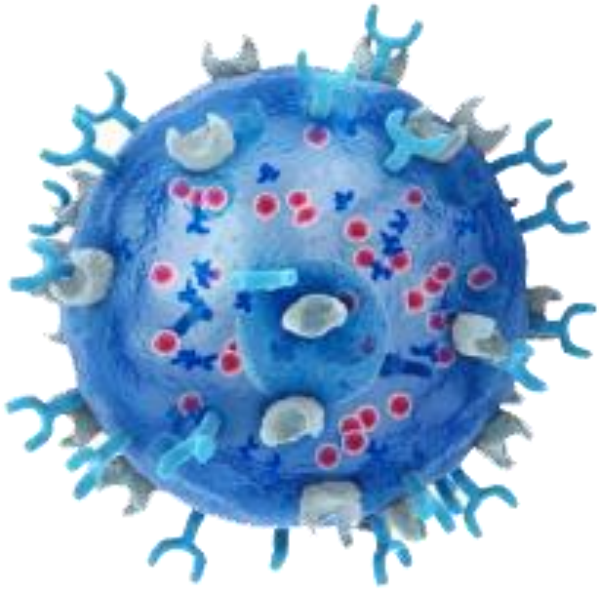
September 4, 2025
Increased ALC: 1,400

Complete Response Non-Hodgkin's Lymphoma (Waldenstroms)

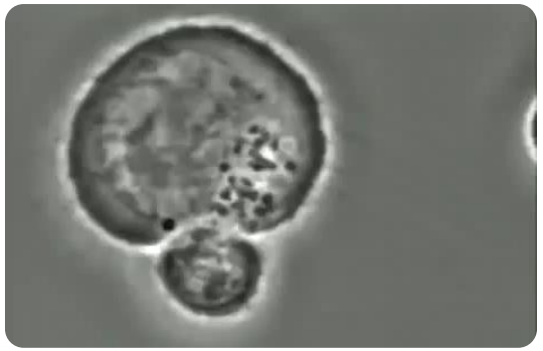


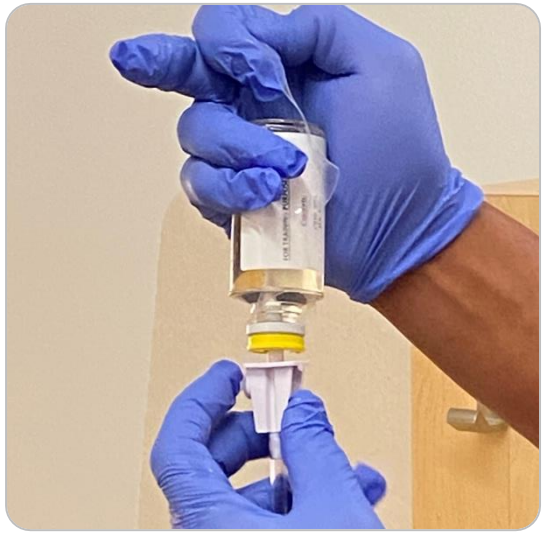
May 6, 2025 July 10, 2025

ANKTIVA + CAR-NK Cellular Therapy



CD19 CAR-NK Cellular Therapy





Outpatient Infusion

Preventive Cancer Vaccine

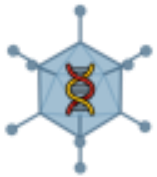
2025

NCI Sponsored, Phase 2 Preventative Cancer Vaccine for Lynch Syndrome

Anktiva + Ad5 CEA/MUC1/Brachyury Vaccine (Tri-Ad5)

Enrollment Completed 2025

DNA Vaccine



Adenovirus (hAd5)

hAd5 CEA, MUC1, Brachyury

hAd5 PSA

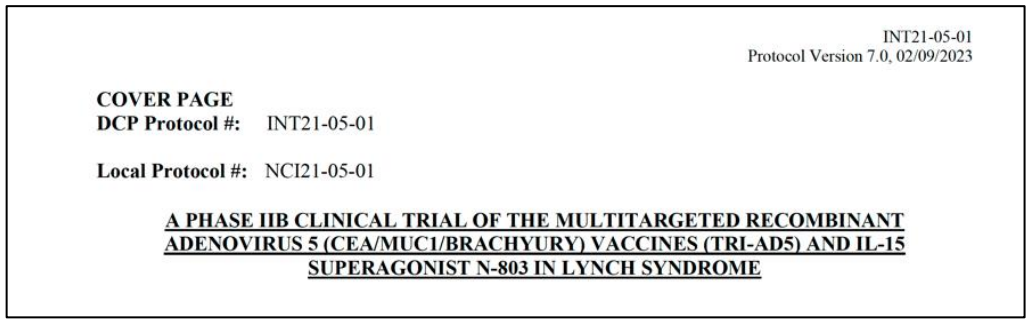
hAd5 HPV

Phase 2

In-Vivo Lymphocyte Training

NIH NATIONAL CANCER INSTITUTE Division of Cancer Prevention

Investigator Initiated Trial
Clinical Trials: NCT05419011



INT21-05-01
Protocol Version 7.0, 02/09/2023

COVER PAGE
DCP Protocol #: INT21-05-01

Local Protocol #: NCI21-05-01

A PHASE IIB CLINICAL TRIAL OF THE MULTITARGETED RECOMBINANT ADENOVIRUS 5 (CEA/MUC1/BRACHYURY) VACCINES (TRI-AD5) AND IL-15 SUPERAGONIST N-803 IN LYNCH SYNDROME

NIH National Cancer Institute
Northwestern University
KU Medical Center — The University of Kansas
The University of Texas MD Anderson Cancer Center
Mayo Clinic
University of Michigan
UCSF
University of Colorado Anschutz Medical Campus
Cleveland Clinic
The University of Arizona Cancer Center
Universidad de Puerto Rico
Fox Chase Cancer Center — Temple Health
Dana-Farber Cancer Institute
City of Hope
Carbone Cancer Center — University of Wisconsin School of Medicine and Public Health
The Ohio State University — Wexner Medical Center
The University of Chicago

- Lynch syndrome affects approximately **1 in 279 individuals** in the general population based on large unselected sequencing cohorts, making it far more common than previously recognized.
- A global analysis suggesting a worldwide prevalence of **2 to 3 million people** living with Lynch syndrome. 80% increased risk of colon cancer
- Approximately **3 to 5 percent** of all colorectal cancers and **2 to 6 percent** of endometrial cancers arise from Lynch syndrome, making it a major contributor to preventable malignancy.

NK Cell Activation Together with T Cells Demonstrated Complete Remission in Late-Stage Tumors Across Multiple Tumor Types

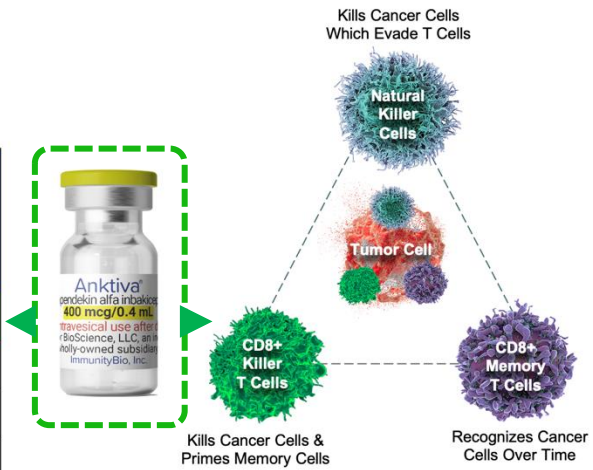
DURABLE COMPLETE RESPONSES

- **NMIBC: BCG Naïve**
  Complete remission lasting over 9 years
- **NMIBC: BCG Unresponsive**
  Complete remission lasting over 54+ mo
- **Merkel Cell Carcinoma**
  Complete remission lasting over 6 years
- **Non-Hodgkin's Lymphoma**
  Complete remission lasting over 2 years
- **Metastatic Pancreatic Cancer**
  Complete remission lasting over 3 years
- **Triple Negative Breast Cancer**
  Complete remission lasting 2 years
- **Head & Neck Cancer**
  Complete remission lasting over 2 years

ANKTIVA as the Backbone for Universal Cancer Immunotherapy

NMIBC Bladder BCG Unresponsive	NMIBC Bladder Naïve	Merkel Cell Carcinoma	Non-Hodgkin's Lymphoma	Triple Negative Breast Cancer	Head & Neck	Pancreatic Cancer
Complete Response	Complete Response	Complete Response	Complete Response	Complete Response	Complete Response	Complete Response
ANKTIVA	ANKTIVA	ANKTIVA	ANKTIVA	ANKTIVA	ANKTIVA	ANKTIVA
BCG	BCG	aNK	Rituximab	PD-L1 Chemo	PD-L1 Chemo	PD-L1 Chemo
NCT03022825	NCT02138734	NCT02465957	NCT02384954	haNK	haNK	PD-L1 t-haNK
				Adeno	Adeno	Adeno
				NCT03387085	NCT03387111	spIND

FDA Approved April 2024



Activating the host's immune system with proliferation of the natural killer and killer T cells provides the potential for a universal cancer therapy regardless of tumor types

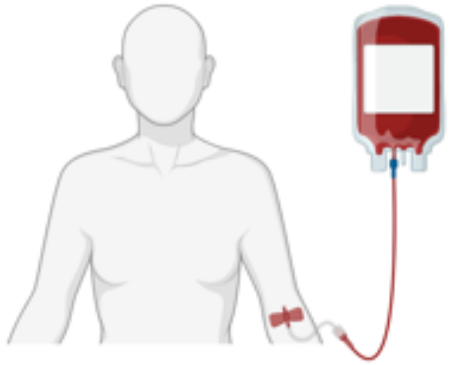
With 2024 approval, the potential for ANKTIVA to be the foundational IL-15 cytokine activating natural killer cells and killer T cells with resultant complete remission even in late-stage advanced tumors across multiple tumor types

The Future 2026+

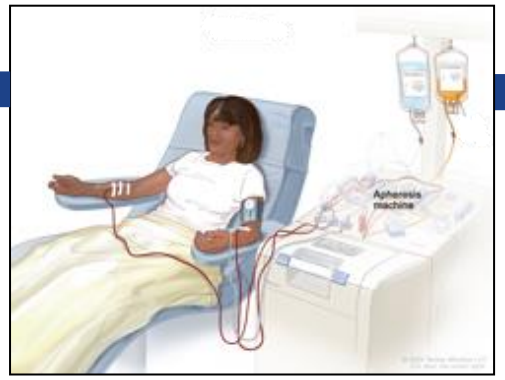
Harnessing AI in Discovery and Manufacturing

Cell Therapy

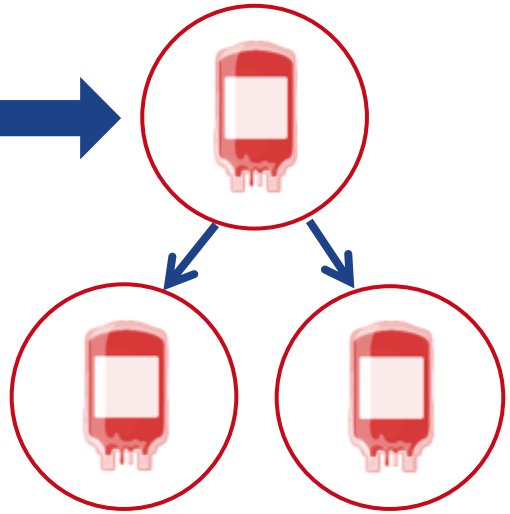
Apheresis Program: Autologous / Allogenic Cellular Vaccine Therapy Program



Apheresis
Cancer Vaccine



Single Apheresis



Non-Cryopreserved
(Fresh) Apheresis

T Cell Pathway

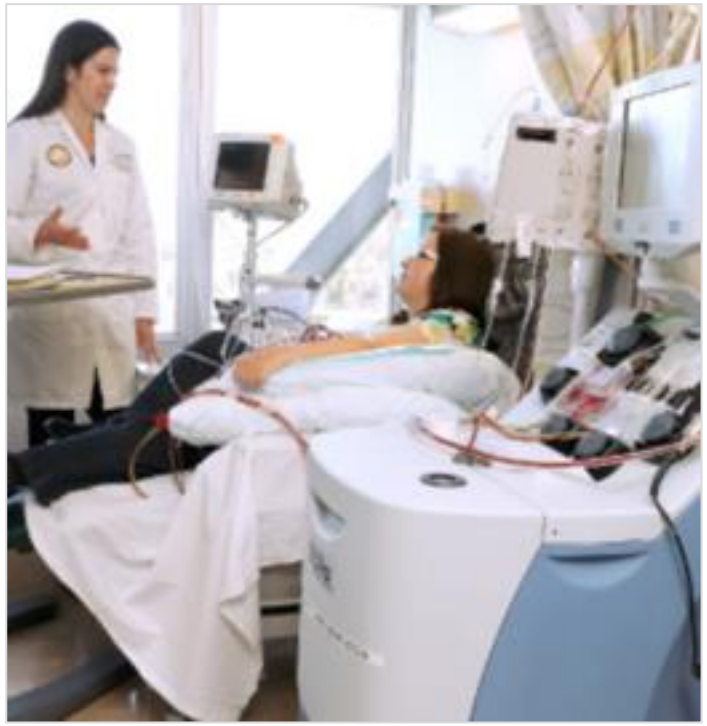
Gamma Delta T Cell

NK, iNKT & Dendritic Cell Pathway

M-ceNK
iNKT

Memory-Like Cytokine Enhanced Natural Killer (M-ceNK) Cells from Peripheral Blood: First-in-Human Clinical Trials

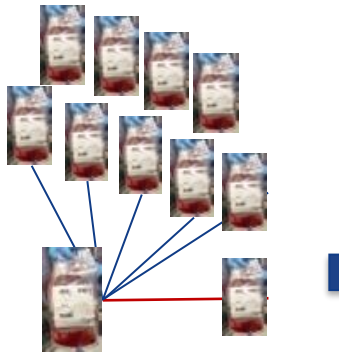
Day 1



Autologous Apheresis
Patient White Cell Collection

Day 1

Autologous
Apheresis
White Cells



Single Aliquot
For Enrichment

Aliquot One Bag into
10 Lots for
Cryopreservation

Day 17

Concentrate
0.3 – 1.0 x 10^9 NK Cells

Day 17

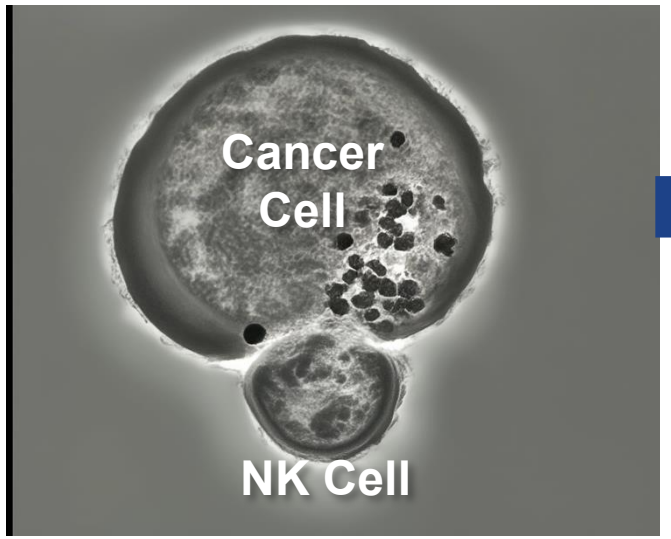
Autologous Cytokine
Enhanced Natural Killer Cells
for Transfusion
0.3 – 1.0 x 10^9 NK Cells

The World's First AI Driven CAR-T and CAR-NK Manufacturing

Reducing the Cost and Providing Access of Cellular Therapy at Global Scale

Next Generation Single Chain Antibodies ‘Nantibodies’

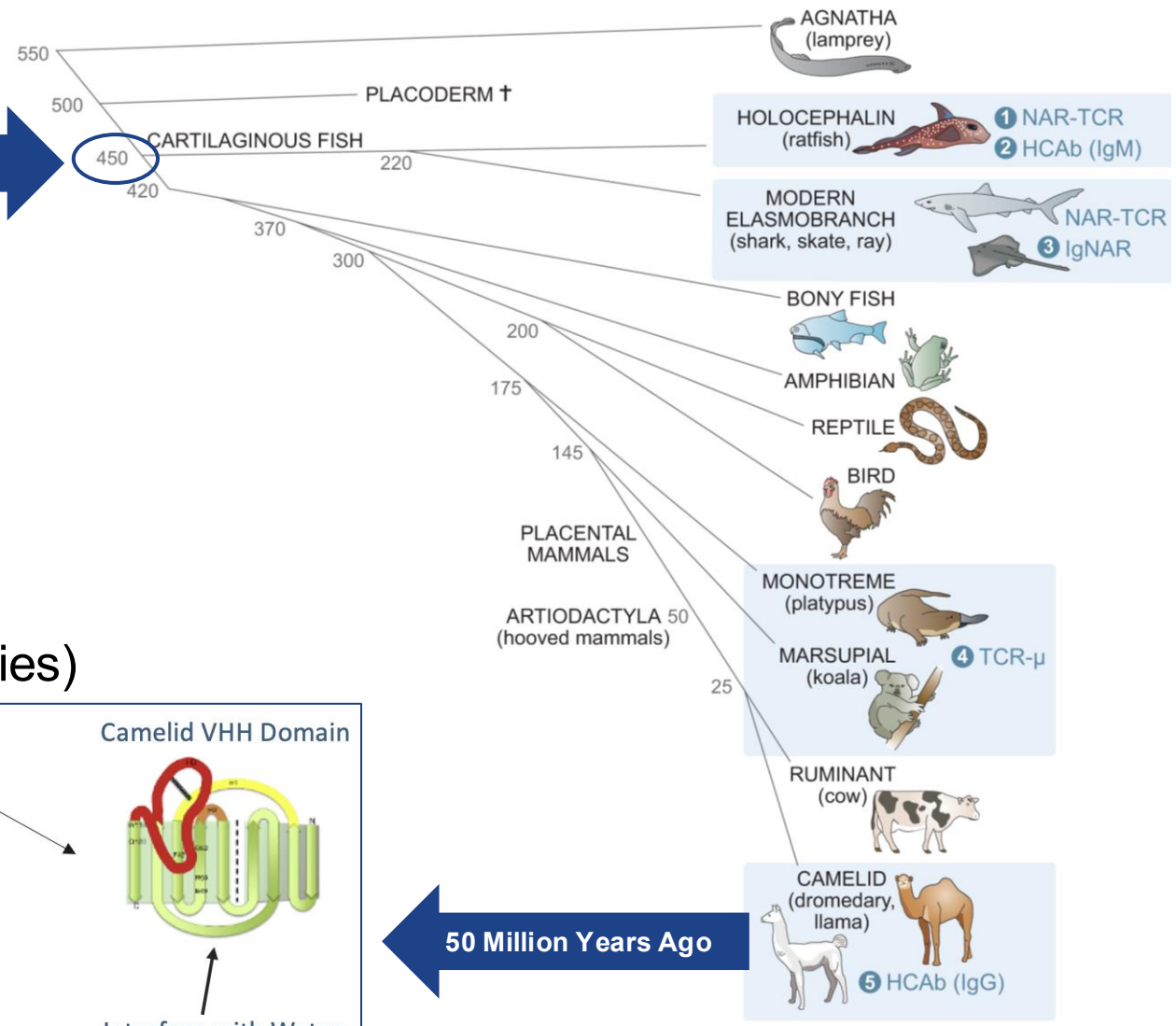
Enlighted by Evolution: NK Cells & Single Chain Antibodies



The Natural Killer (NK) Cell

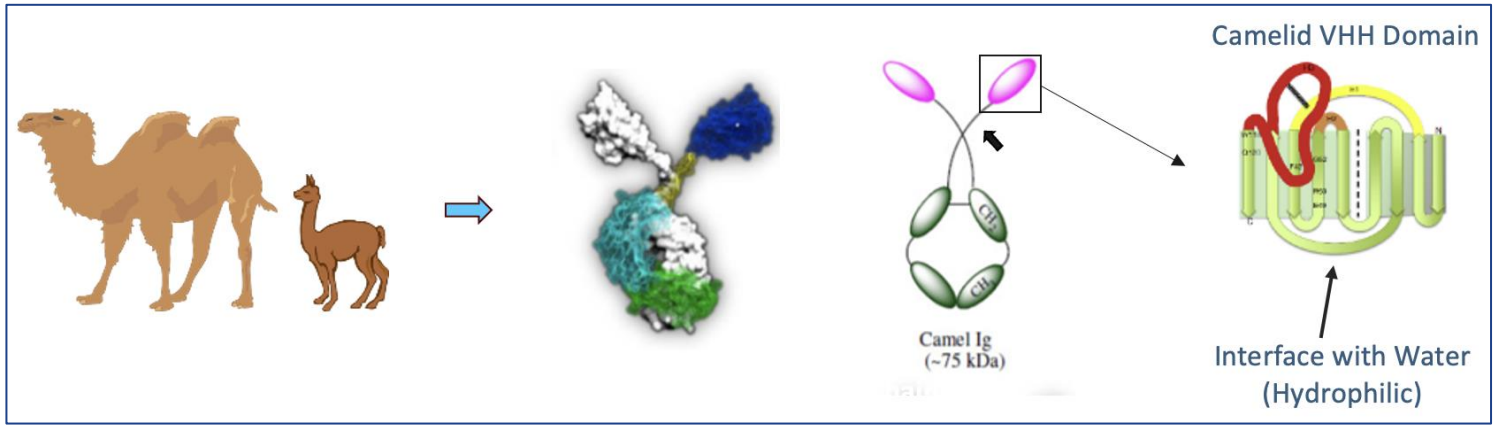
The Evolution of the Natural Killer Cell

450 Million Years Ago

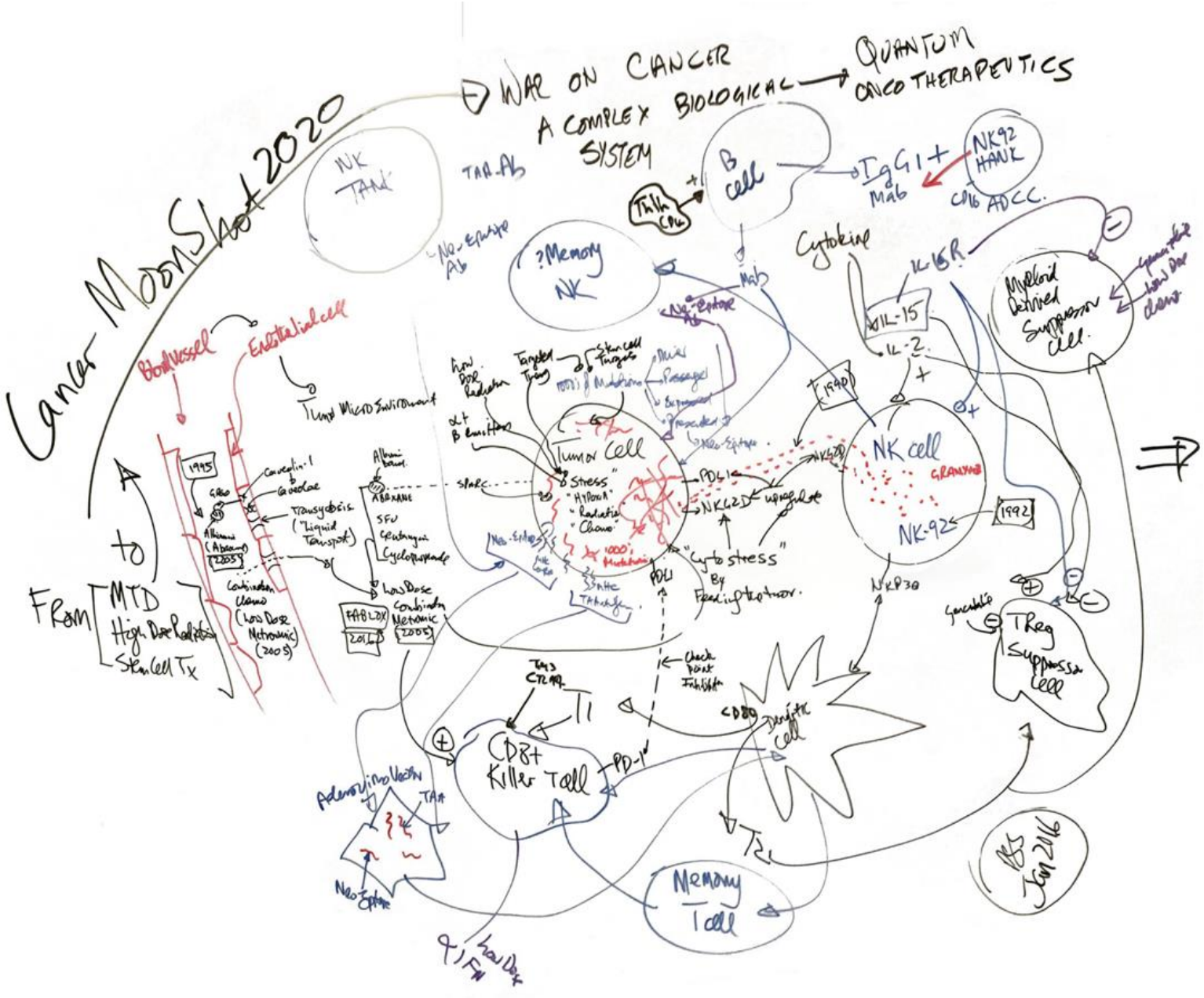


50 Million Years Ago

Single Chain Antibodies (Nantibodies)



Winning the War Against Cancer: Harnessing the Power Within



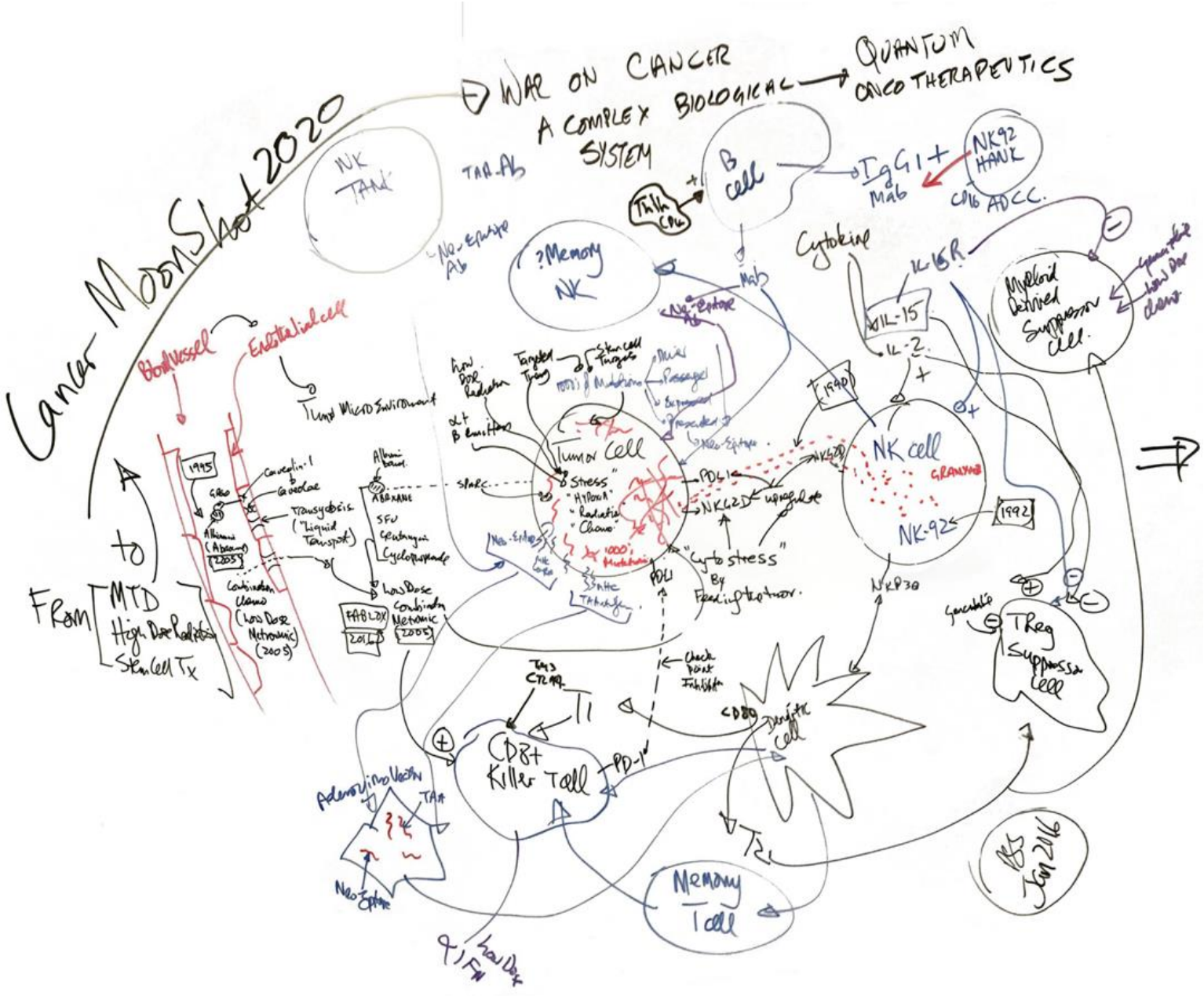
“The Cancer Vaccine”

Hypothesis:
Orchestrating the innate and adaptive immune system drives immunogenic cell death with durable complete remission of cancer independent of tumor type

Presented to FDA, Oncology Center of Excellence (OCE) 2016

PSS Mind Map Jan 2016

The Cancer Vaccine



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Quantum Oncotherapeutics
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https://bit.ly/3Op84wi