National Cancer Institute

Clinical development of immunotherapies

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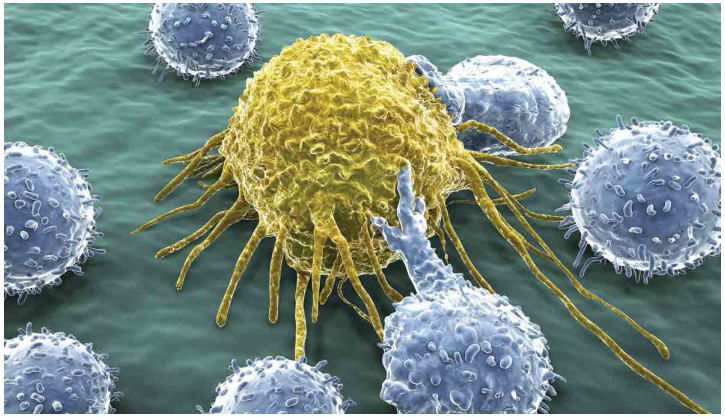
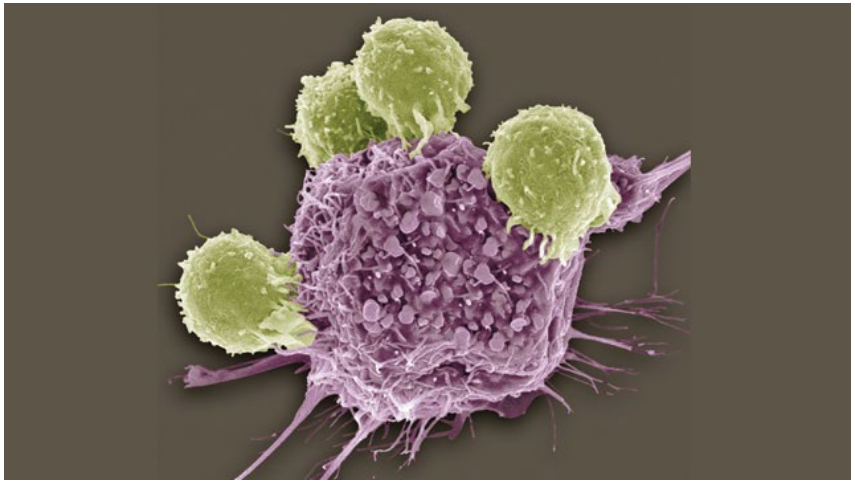




2021 NCI Drug Development Workshop
How to Advance A Therapeutic Candidate from Bench to Bedside

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Goals*

- Historical perspective
- Re-familiarization of the principles of Cancer Immunology
- Range of Agents
- Creating a framework for IO clinical development

* These are personal perspective and does not represent NCI policy

Historical Perspective

- Observations
- Historical Narratives

Cancer Treatment Paradigms: Theory to Therapy

Hypothesis: Radiation damage can Treat Cancer 19-20th Century

1896: E. Grubbe: Rx of breast cancer
1909: C. Regaud: Chromatin target of XRT
1922: H. Coutard: Fractionated XRT

Hypothesis: Surgery as curative intent 19-20th Century

1882: W. Halsted: Sufficient Local Removal of the tumor to cure cancer
1954: O. Wangensteen: Rescue benefit with metastatectomy
1958: B. Fisher: Cancer's metastatic behavior dictates outcome and thus less surgery is more
1995: S. Hellman & R. Weichselbaum: Oligometastasis hypothesis

Hypothesis: Unencumbered cell division causes cancer: Inhibit tumor cell division – Chemotherapy 20th Century

1940: L. Goodman & A. Gilman – Nitrogen Mustard
1948: S. Farber: Anti-Folate
1955: National Cancer Chemotherapy Service Center
1965: J. Holland, E. Freirech, E. Frei: Combination chemotherapy

Hypothesis: Molecular drivers of cancer: Inhibit tumor driver pathway – Targeted therapy 21st Century

1941: C. Huggins and C. Hodges: Testosterone inhibition CaP
1971: M. Cole: anti-estrogens in BrCa
2001: B. Druker: Inhibition of BCR-ABL by TKI in CML

Hypothesis: Immune therapy for cancer: Immune recognition and destruction of cancer– 18th - 21st Century

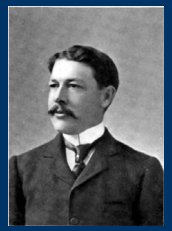
Immunotherapy for Cancer: Induce inflammation
A 18th and 19th Century Paradigm

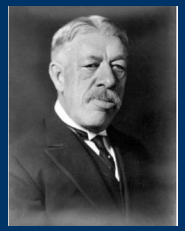
1768: G. White: Use of poultice made from decaying toads for breast cancer

1844: S. Tanchou: Treatise on breast cancer: spontaneously or induced Gangrene as a therapeutic agent in cancer

1886: A. Verneuil: Suppuration after surgery; Congress of Surgery Paris

1891: W.B.Coley: Annals of Surgery describing Toxins: Initially used deliberate infection and in 1893 he began combining killed *Streptococcus pyogenes* and *Serratia marcescens* ---- *1985 mammalian TLR*





Dr. William B. Coley (1862-1936)

Chief of the Bone Sarcoma Unit at Memorial Hospital in New York

Historical Development of Interferon

- First described by Yasu-ichi Nagano and Yasuhiko Kojima 1954 reported in French (Seances Soc. Biol. Fil). - viral inhibitory factor
- Independently described by Alick Isaacs and Jean Lindenmann in 1957 (J Proc. Roy. Soc. Lond. B Biol. Sci) – coined the term interferon

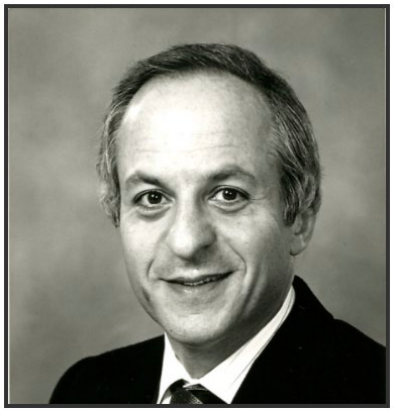
1960 Space Phase I Unit: Interferon

Interferon The Room Where it Happened 1979

Mathilde Krim

Mary Lasker - $1M
Lasker Foundation

Frank Rauscher $1M
NCI



Jordan Guttermann
MDAC

Medical News

December 28, 1979

At year's end, what's new with interferon?

Last year the American Cancer Society (ACS) announced that it was spending $2 million to purchase 40 billion units of interferon from the Finnish Red Cross, enough for American oncologists to study interferon's anticancer activity in about 150 patients.

on widely available. The current price is high because all present methods involve collecting interferon from supernatant fluids of cells grown in culture, a time- and space-intensive procedure.

This same problem, combined with inevitable losses

ACS commitment of
$2M

Immunology captures the Public Interest

New York Times - July 29, 1908

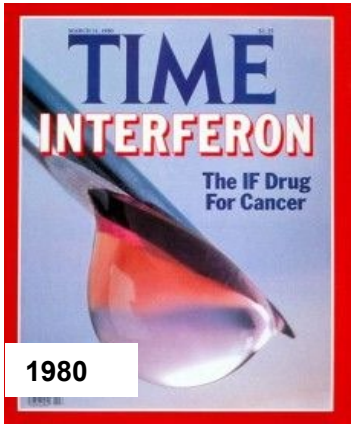
ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

1973



1980

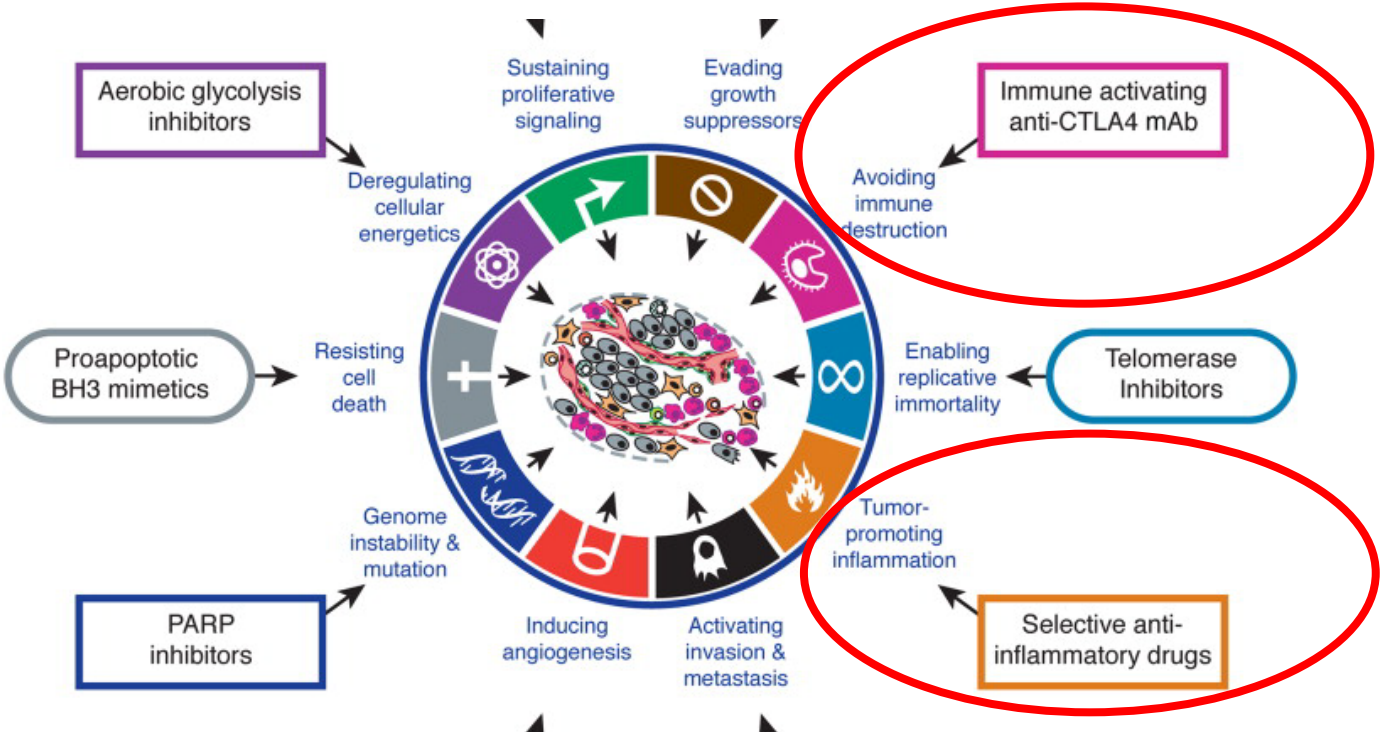
2013

2016

National Cancer Institute

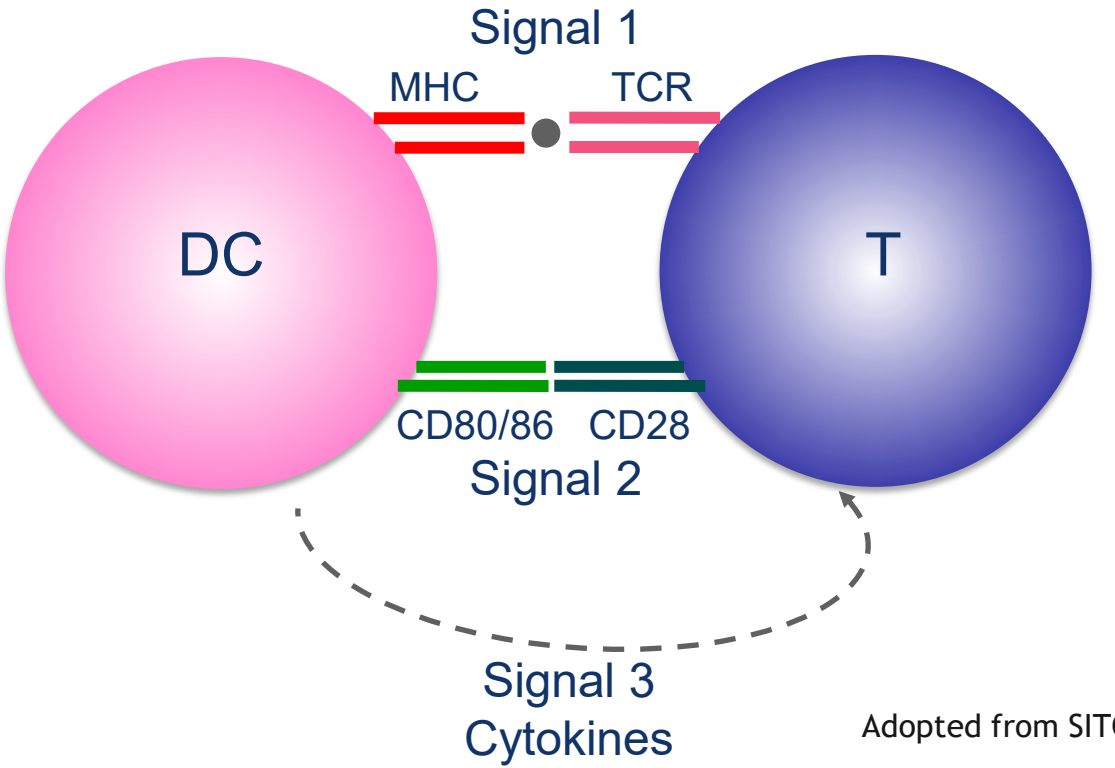
Principles of Cancer Immunology

Summary of the Hallmarks of Cancer



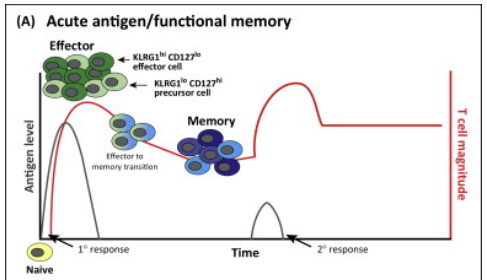
Hanahan & Weinberg: Cell 2011

Activation of a T Cell



Adopted from SITC

Basic Immunology: Immune Response Kinetics



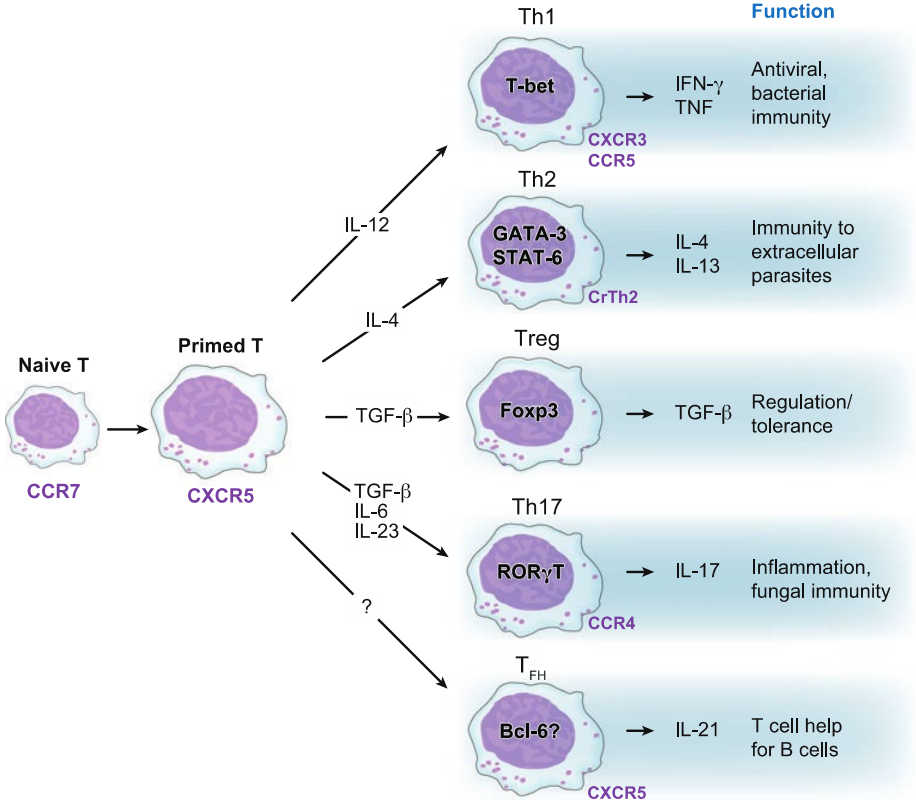
(C)

	Memory	Exhausted	Reinvigorated
Proliferative potential	+++	+/–	++
Cytokine production	+++	+	++
Killing capacity	+++	+/–	++
Dependence on antigen for persistence	–	+++	?
Responsiveness to IL-7/IL-15	+++	–	?

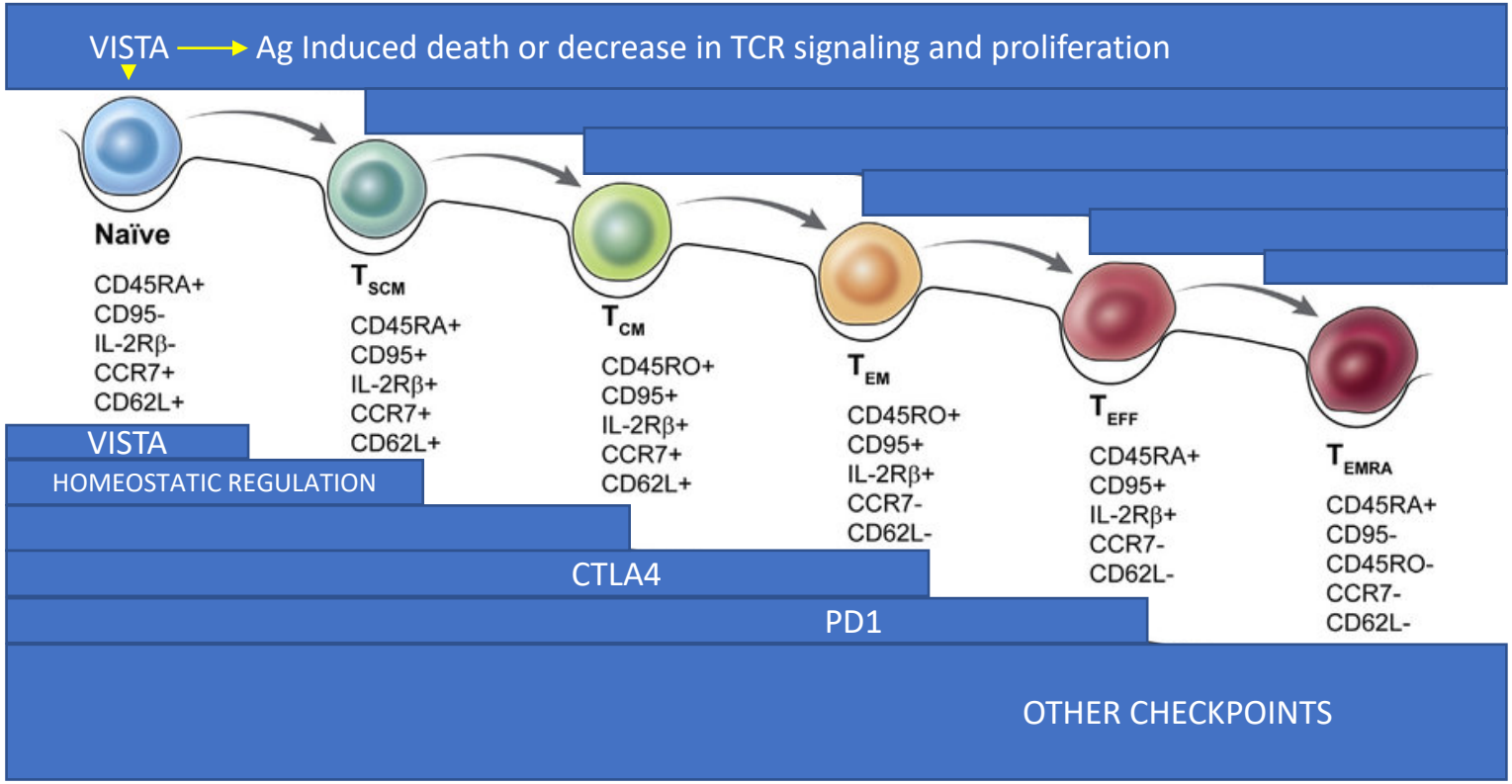
TRENDS in Immunology

Pauken & Wherry
Trends in Immunology
2015

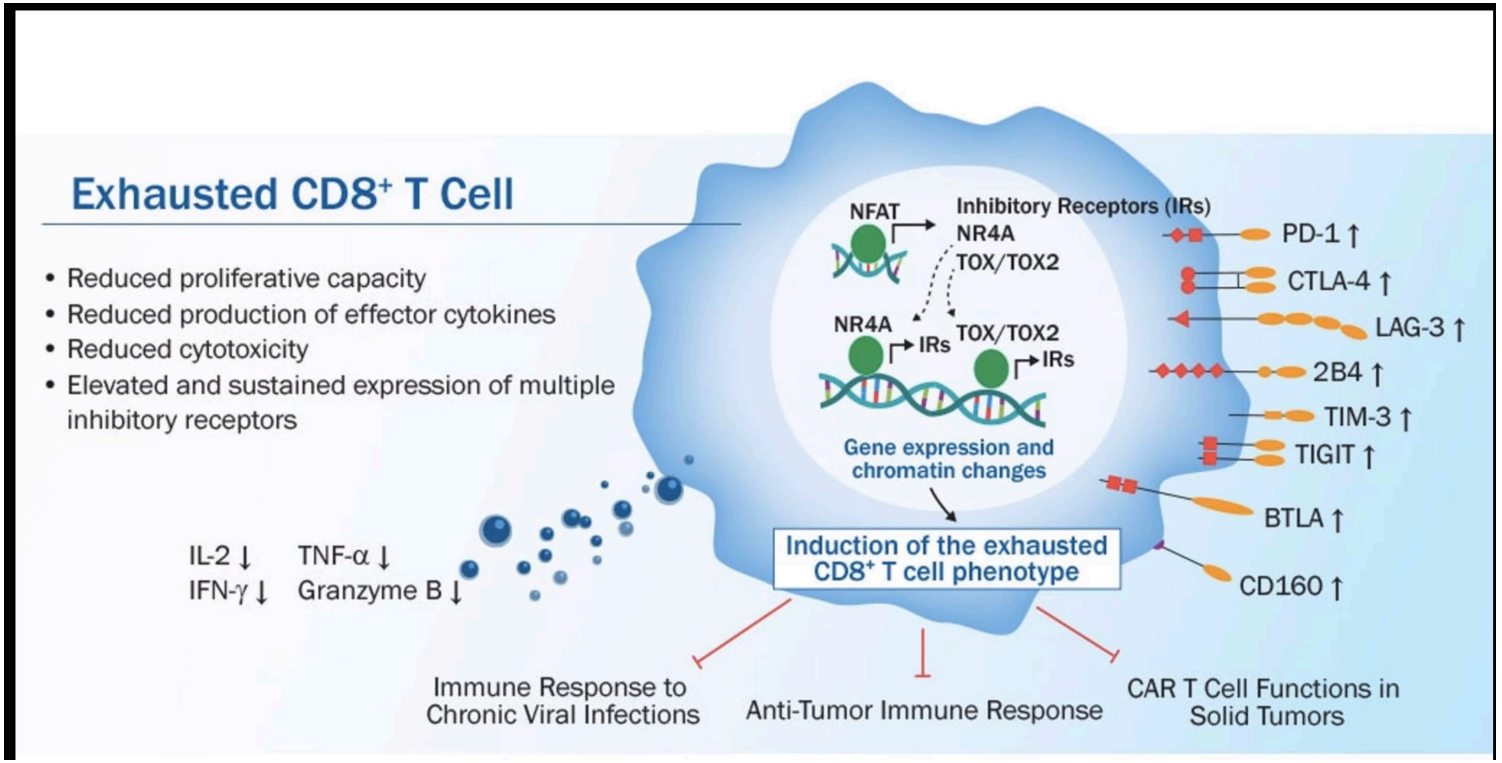
CD4 Differentiation to Effector Cells



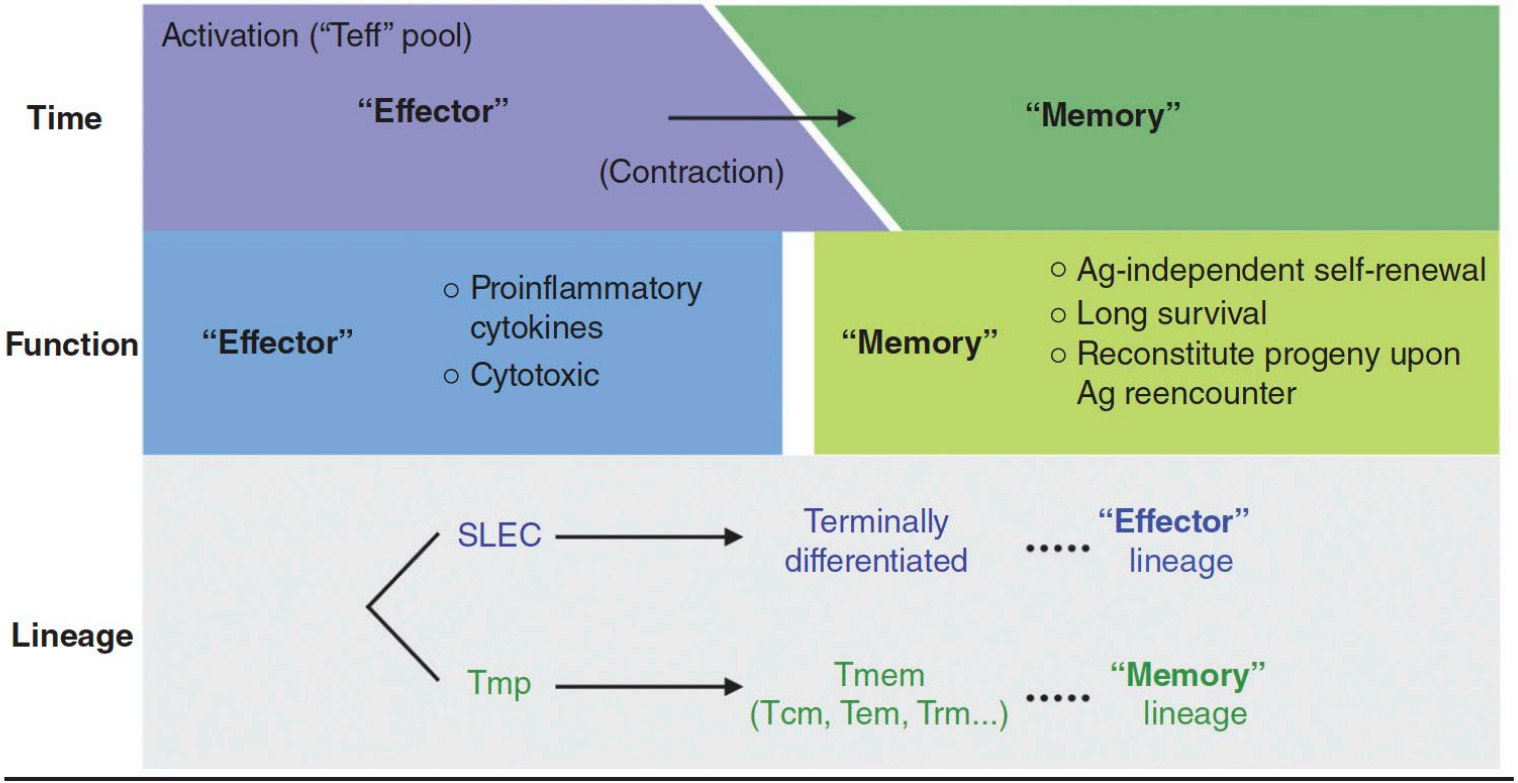
Hierarchical Expression of CD8 T Cell Immune Checkpoints



Adapted from Kishton RJ, Sukumar M, Restifo NP, Cancer Metabolism Review, 2017.


Exhausted CD8+ T Cell
• Reduced proliferative capacity
• Reduced production of effector cytokines
• Reduced cytotoxicity
• Elevated and sustained expression of multiple inhibitory receptors
NFAT
Inhibitory Receptors (IRs)
NR4A
TOX/TOX2
NR4A
IRs
TOX/TOX2
IRs
Gene expression and chromatin changes
Induction of the exhausted CD8+ T cell phenotype
PD-1 ↑
CTLA-4 ↑
LAG-3 ↑
2B4 ↑
TIM-3 ↑
TIGIT ↑
BTLA ↑
CD160 ↑
IL-2 ↓
TNF-α ↓
IFN-γ ↓
Granzyme B ↓
Immune Response to Chronic Viral Infections
Anti-Tumor Immune Response
CAR T Cell Functions in Solid Tumors

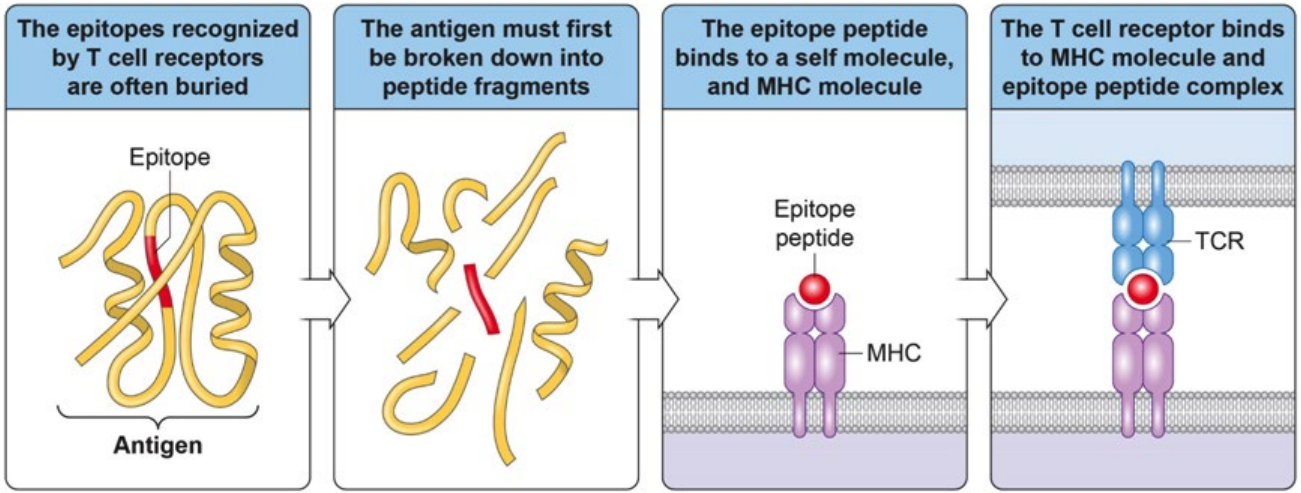
Heterogeneity Model of CD8 T cells



SLEC: Short lived effector cells
Tmp: T memory precursors

Yuki Muroyama & E. John Wherry 2021

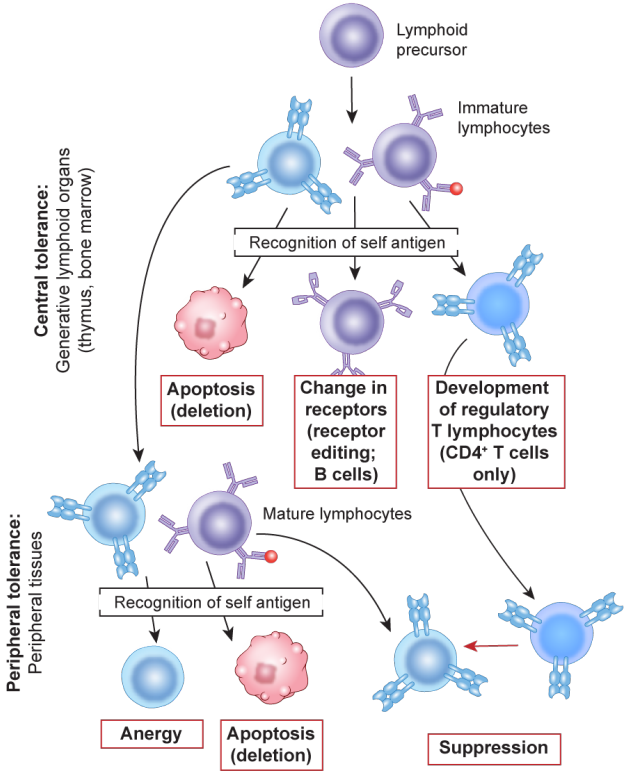
Antigen (protein) Presentation



MHC = Major Histocompatibility Complex

Lipid antigens presentation to T cells through CD1 (related to the class I MHC molecules)

Central and Peripheral Tolerance



Central Tolerance

- For T cells it occurs in the thymus
- Some survive as regulatory (suppressor) T cells while others escape to peripheral tissues

Peripheral Tolerance

- Self-reactive T cells are suppressed by regulatory T cells
- CTLA-4 and PD-1, among other molecules play a role in maintaining self-reactive T cells from becoming activated (anergic)

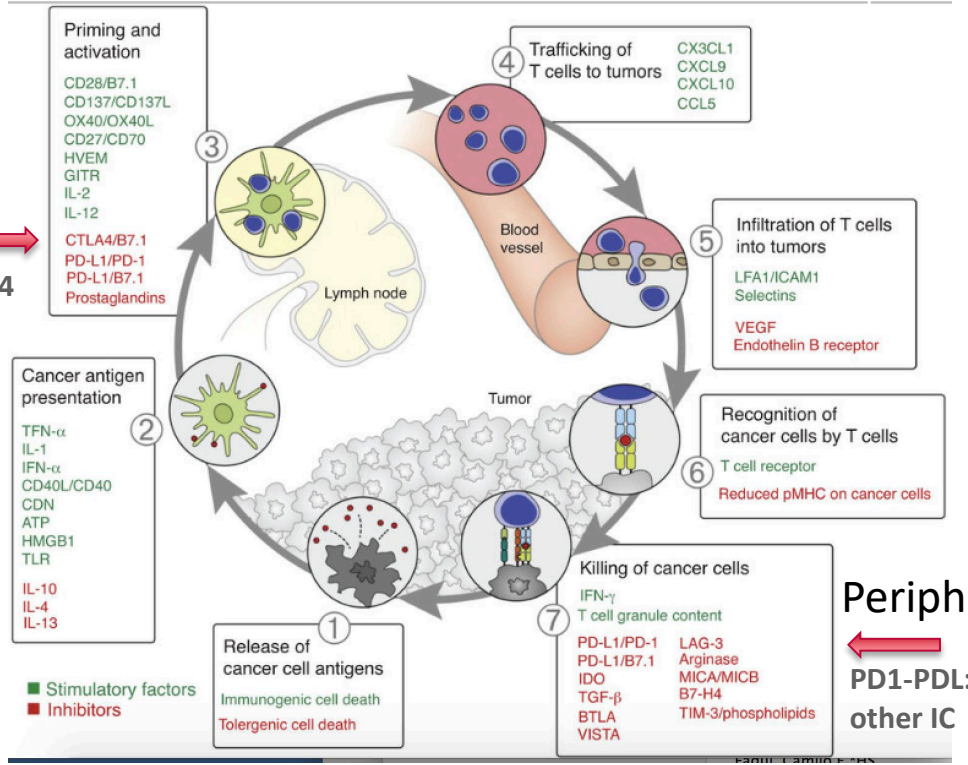
Adopted from SITC

Immune Cycle
Locations of Immune Checkpoint Control

From Chen & Mellman

Central

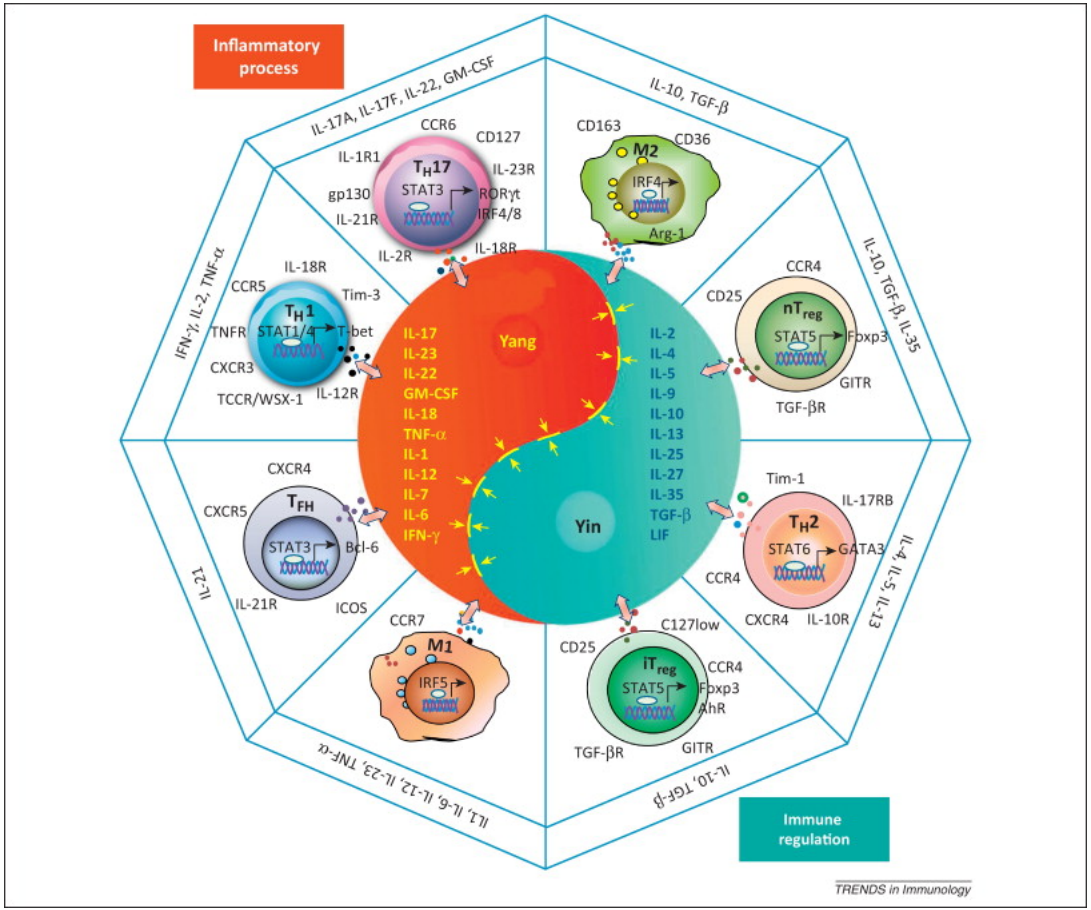
CTLA4



Peripheral

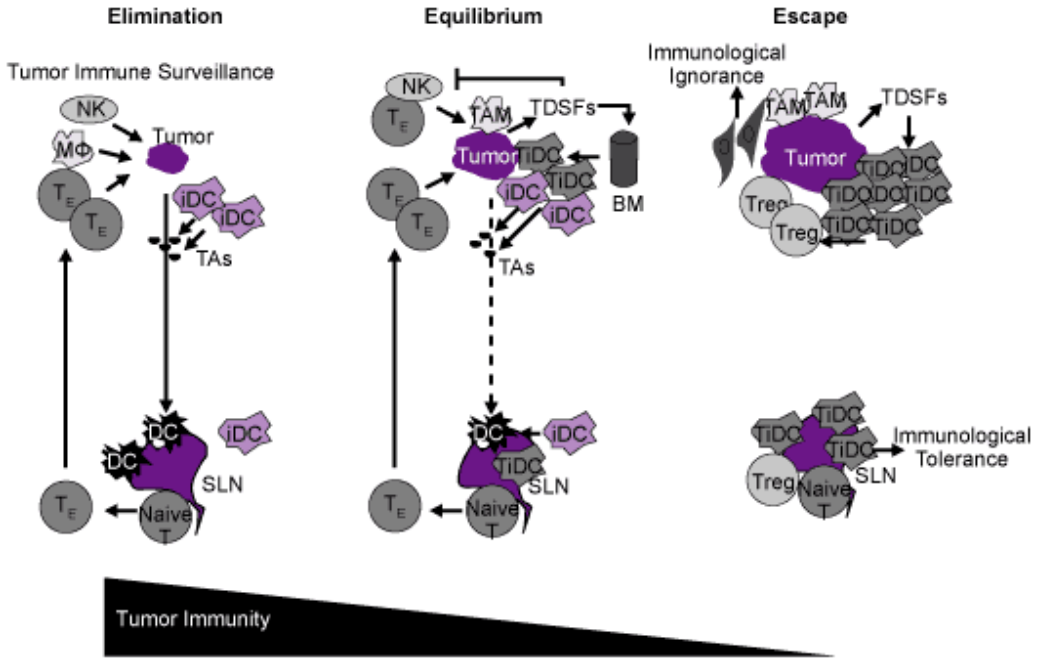
PD1-PDL:
other IC

Systemic and TME Components



Tumor Immungenicity: Immune Surveillance & Immunoediting

Ehrlich 1909
Burnet and Thomas 1957
Schreiber 2002



BM, bone marrow; iDC, immature dendritic cell; Mj, macrophage; SLN, sentinel lymph node; TAM, tumor-associated macrophage; TAs, tumor antigens; TDSFs, tumor-derived soluble factors; TE, effector T cell; TiDC, tumor-associated iDC; Tregs, regulatory T cells.

From FS Hodi

Range of Agents

Range of Agents:
The Landscape of Immunotherapy Targets & Agents for Cancer in 2021

Adoptive	Depletion	Antibody	"Kines"	Metobolmes	Environ	Intratumoral	Antigens
T cells	Treg	ICI	IFN α, β, & γ	Adenosine	Gut Microbio	TLRs	Targets Modifcation
NK cells	MDSC	BiTEs/TriTEs	IL-2	Tyrosine (IDO)	Other Microbio	oncolysates	Epigentic Agnets
Dendritic Cells	TAMs	Conjugate	Designed		Adrenergic Stress	Chemokines	Vaccines
CD34 Cells	Lymphodepl ete	Cytokine block	G- & GM-CSF		Glucocortic oid Stress	Cytokines	Germline
Genetic Mod	CAFs	Chemo block	IL-7			Genes	
Allo	Exosomes	Integrin Block	IL-12				
		ATP-idase (CD39, 73)	IL-15				
		ADCC	TNFα				
			IL-10				
			IL-4				

Engineered T cells

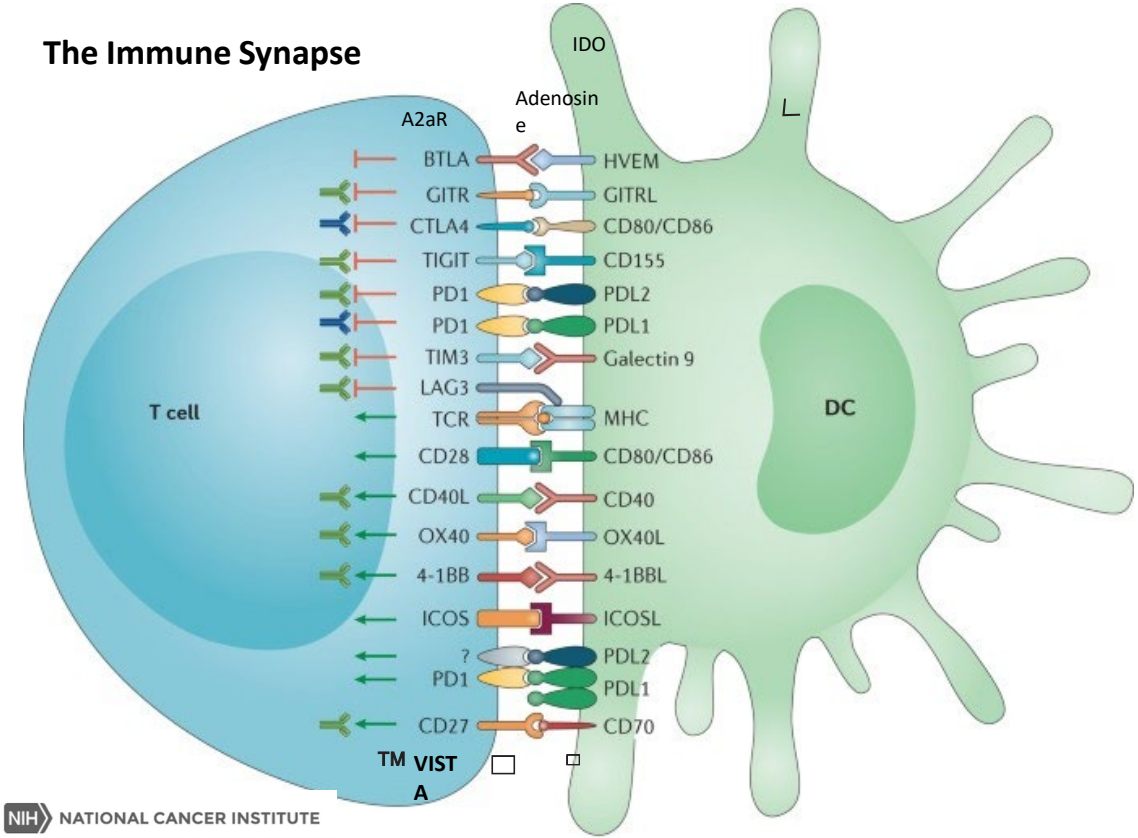
- Chimeric Antigen Receptor
  - Starting with Auto (Allo) T cells
  - CAR engineering
    - MHC independent
    - Receptor/Target Surface
    - Target specificity
    - Transmembrane bridge
    - Humanization of sVC domain
    - Signaling domains
  - Knockout (armored)
    - TCR
    - HLA
    - Other

- TCR T cells
  - Starting with Auto (Allo) T cells
  - Targets can be intracellular immune epitopes
  - MHC specific
  - Target specificity
  - Knockout (armored)
    - TCR
    - HLA
    - Other

Immune Checkpoints

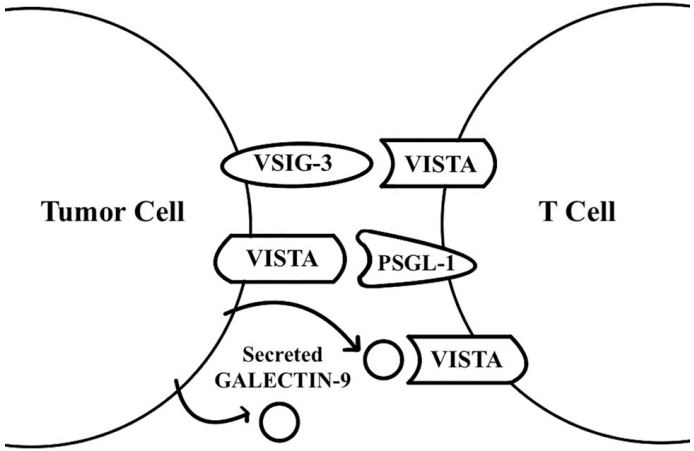
Interactions with antigen-presenting cells that regulate T cell responses

The Immune Synapse



VISTA in the TME

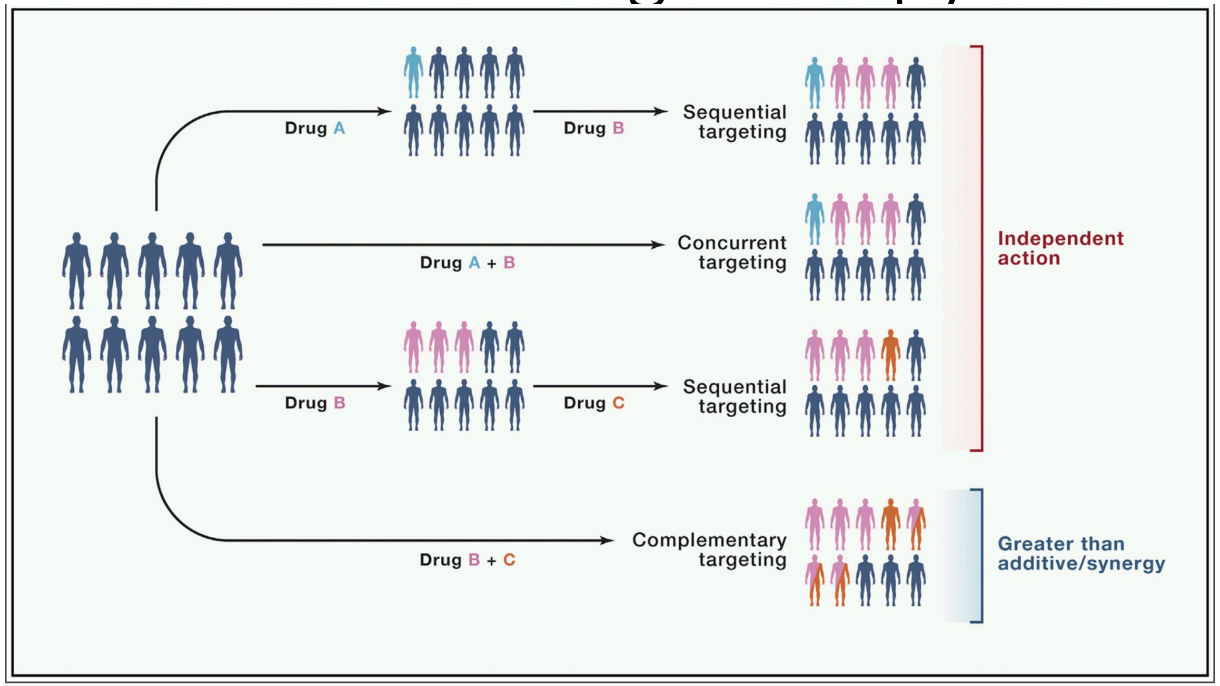
(Yum & Hong 2021)



National Cancer Institute

Creating a framework for IO clinical development

Combination Drug Therapy



Doroshow JH and Simon RM 2017

Adopted from:
Frei & Freireich 1965, Sartorelli 1969, DeVita &Schein 1973, Kummar 2010, Parchmanet & Doroshow 2016

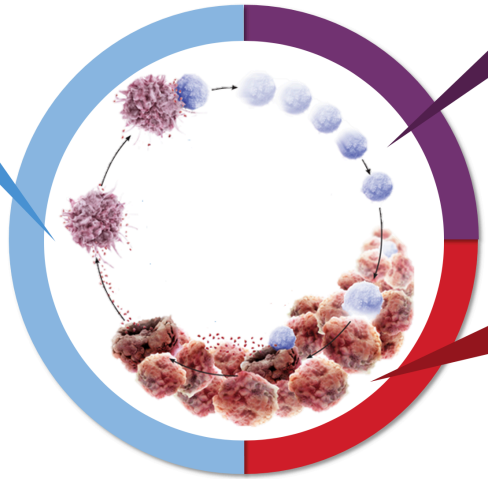
Combination Principles

- Drugs used in combination should cause measurable tumor regressions when employed individually – Not always the case in IO development
- Each ought to demonstrate a different mechanism of action to minimize the development of resistance – IO pathway dependent
- The clinical toxicities of each compound should not overlap to permit their use in effective doses – irAE are common across IO agents
- Intensive intermittent treatment is preferred over continuous, low-dose therapy to enhance cytoreduction - Maintenance of effector cell populations
- Trial designed on systems biology: mechanistic understanding of drug action could facilitate a clinical-rial-design approach based on precise measures of biochemical heterogeneity from patient-derived materials - Ditto for IO

Meckel-Serres Law or Theory of Recapitulation
Ontogeny recapitulates Phylogeny (Haekel)
Applied to Cancer Immunology (Ernstoff 2000)

Antigen → Presentation → Activation → Expansion → Regulation → Trafficking → Exhaustion → Escape → Resistance

Key strategies to reinitiate the anti-tumour immune response according to each phenotype



IMMUNE DESERT

- Generate/release/ deliver antigens
- Enhance antigen presentation and T-cell priming
- Redirect and engage T cells

IMMUNE EXCLUDED

- Recruit T cells to tumour
- Address stromal barrier
- Redirect and engage T cells

INFLAMED

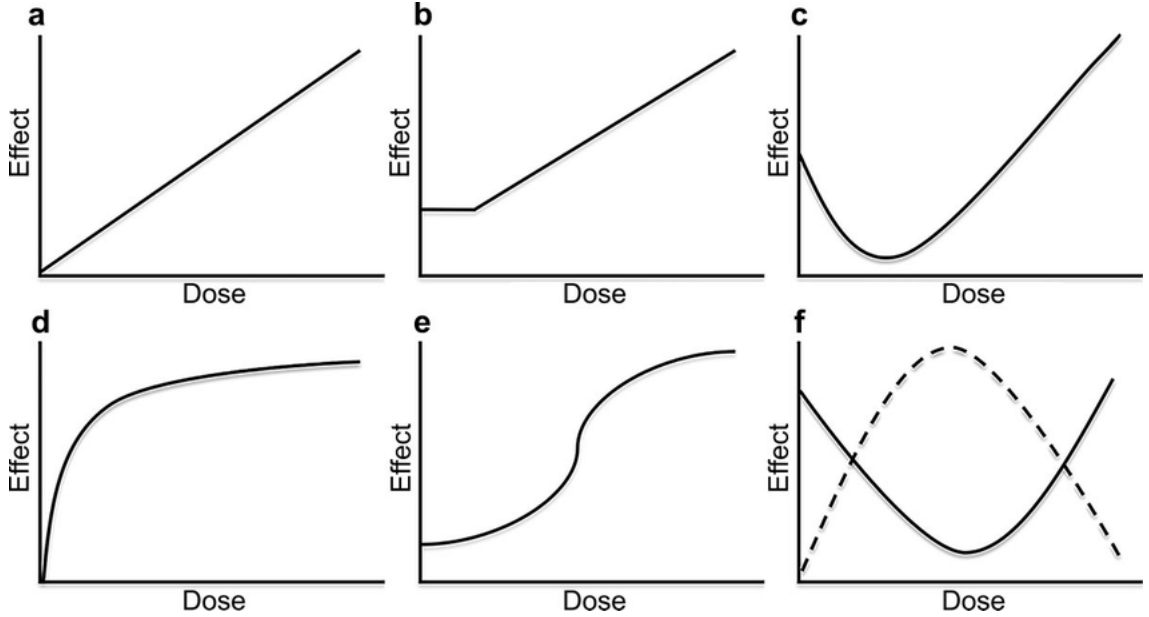
- Invigorate T cells
- Redirect and engage T cells

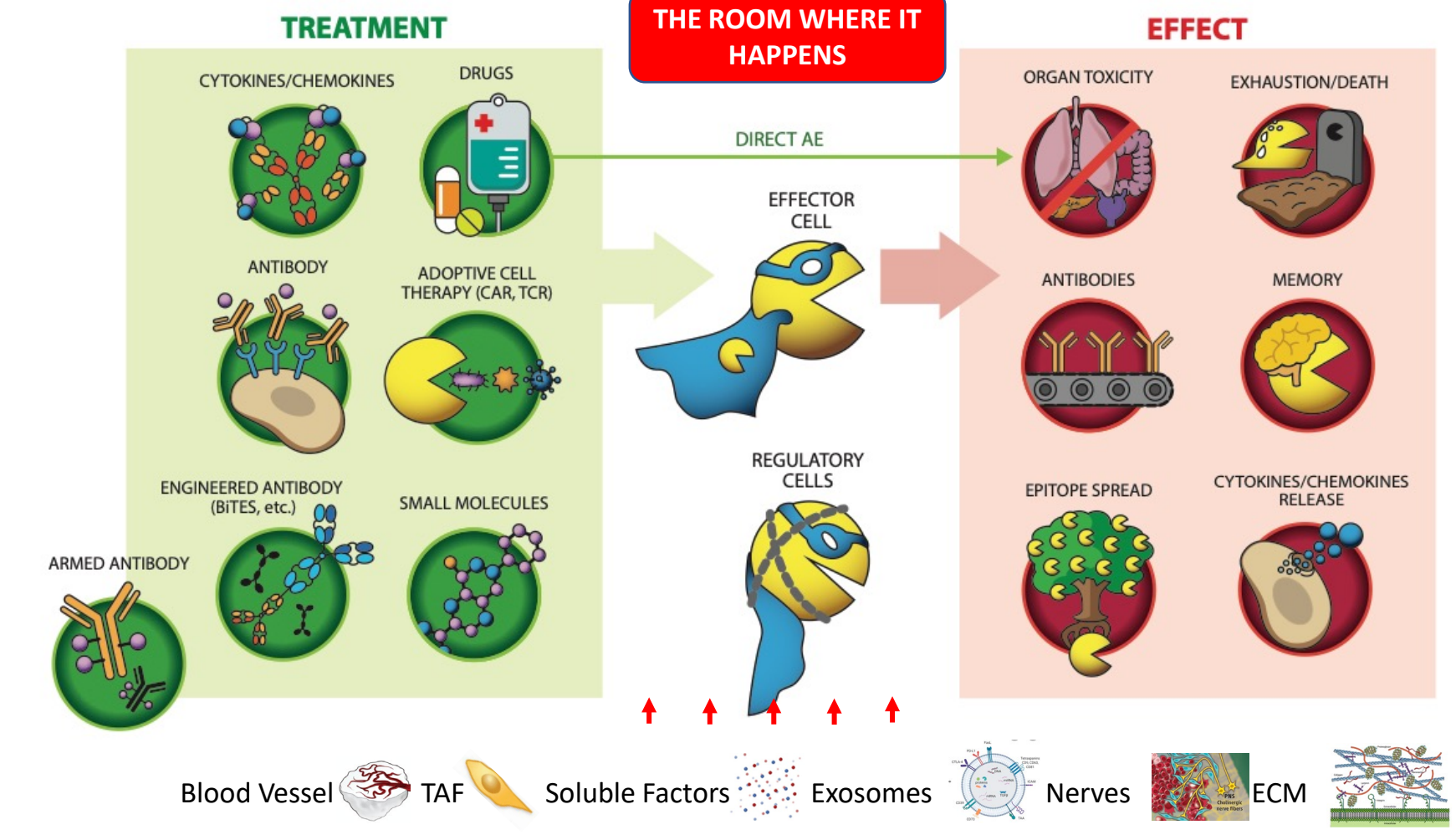
Adapted from 1. Chen DS, & Mellman I. Immunity 2013; 39(1): 1-10; 2. Hedge PS, et al. Clin Cancer Res 2016; 22(8) 1865-1874; 3. Kim JM, & Chen DS. Ann Oncol 2016; 27(8): 1492-1504; 4. Chen DS, & Mellman I. Nature 2017; 541(7637): 321-330.

History of Combination IOs

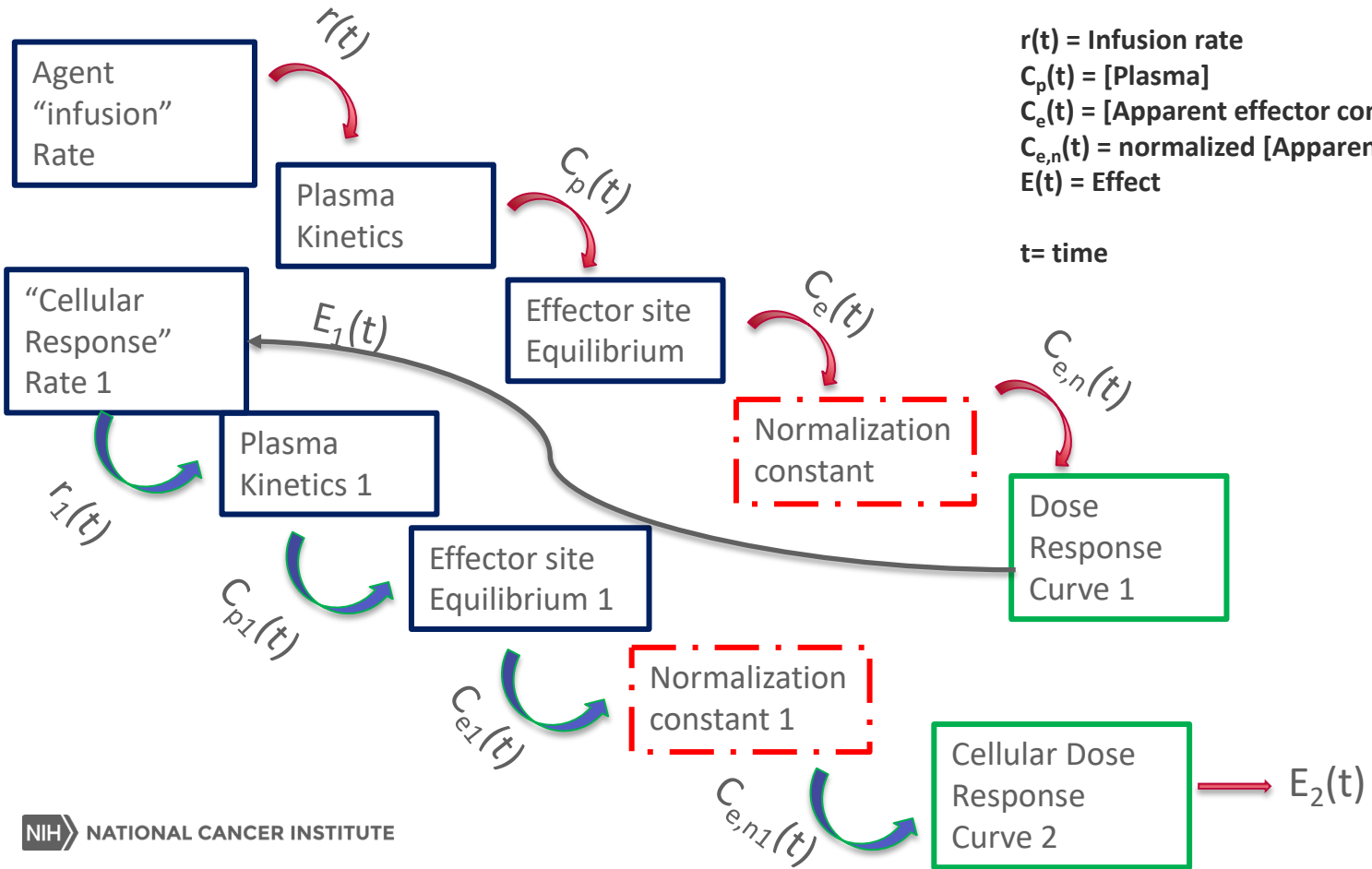
Regimen	Indication	Author	Year
IL-2, ATC	Mel. RCC	Rosenberg	1965
IL-2, IFNa	RCC	Atzopdien	1990
IFNa, IFNg	RCC	Ernstoff	1992
Biochemo	Mel	Ron	1994
IFNb, IL-2	RCC	Witte	1995
BiAb IFNg	Her2+	Lewis	2001
Ipi, IL-2	Mel	Maker	2005
IFNa, Vax	Mel	Mitchell	2007
IFNa, IL-2, Vax	RCC	Schwaab	2009
Ipi, gp100 Vax	Mel	Hodi	2010
Ipi, Nivo	Mel	Wolchock	2013

Dose Response Curve Considerations for IO agents




TREATMENT
THE ROOM WHERE IT HAPPENS
EFFECT
CYTOKINES/CHEMOKINES
DRUGS
DIRECT AE
ORGAN TOXICITY
EXHAUSTION/DEATH
EFFECTOR CELL
ANTIBODY
ADOPTIVE CELL THERAPY (CAR, TCR)
ANTIBODIES
MEMORY
REGULATORY CELLS
ENGINEERED ANTIBODY (BiTES, etc.)
SMALL MOLECULES
EPITOPE SPREAD
CYTOKINES/CHEMOKINES RELEASE
ARMED ANTIBODY
Blood Vessel
TAF
Soluble Factors
Exosomes
Nerves
ECM

Dose Response Considerations for IO agents

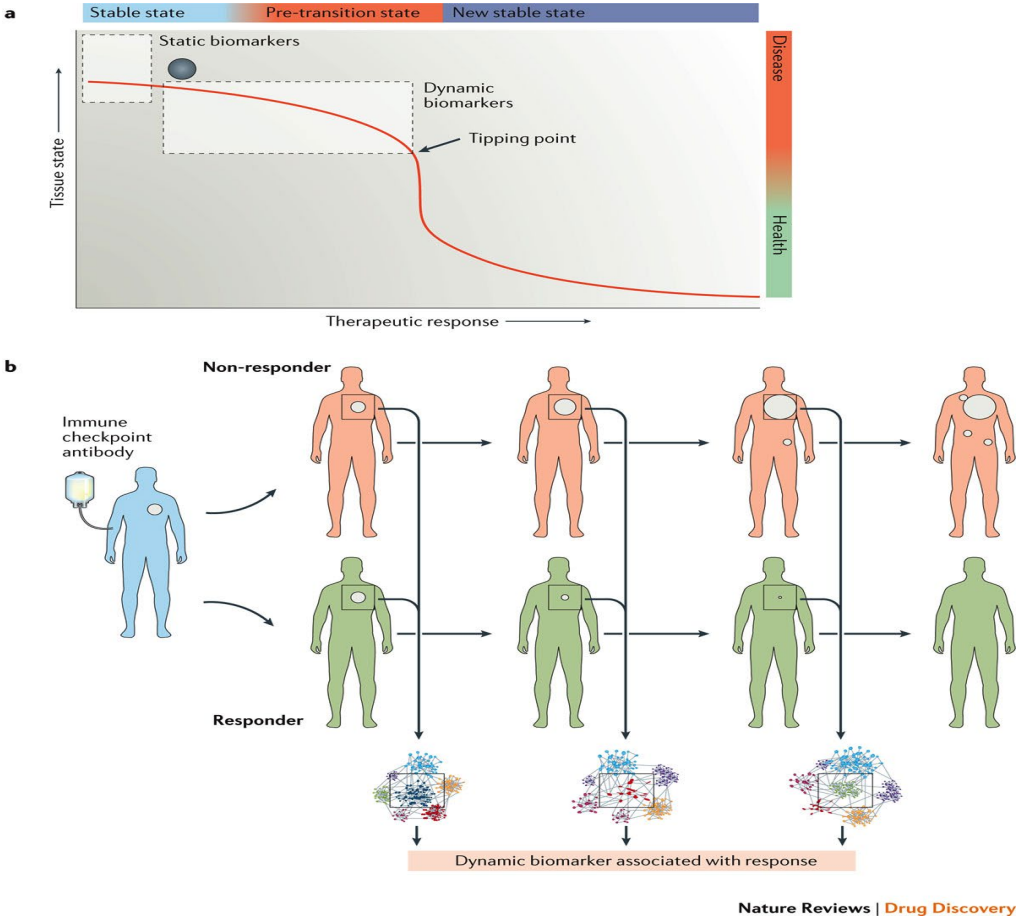


r(t) = Infusion rate
$C_p(t)$ = [Plasma]
$C_e(t)$ = [Apparent effector compartment]
$C_{e,n}(t)$ = normalized [Apparent effector compartment]
E(t) = Effect

t= time

Biomarker Approaches to TME

Lesterhuis et al
Nature Reviews
Drug Discovery
2017



Future Directions for Checkpoint Inhibition
Single Agent Activity, in what setting, Recapitulate Immune pathways

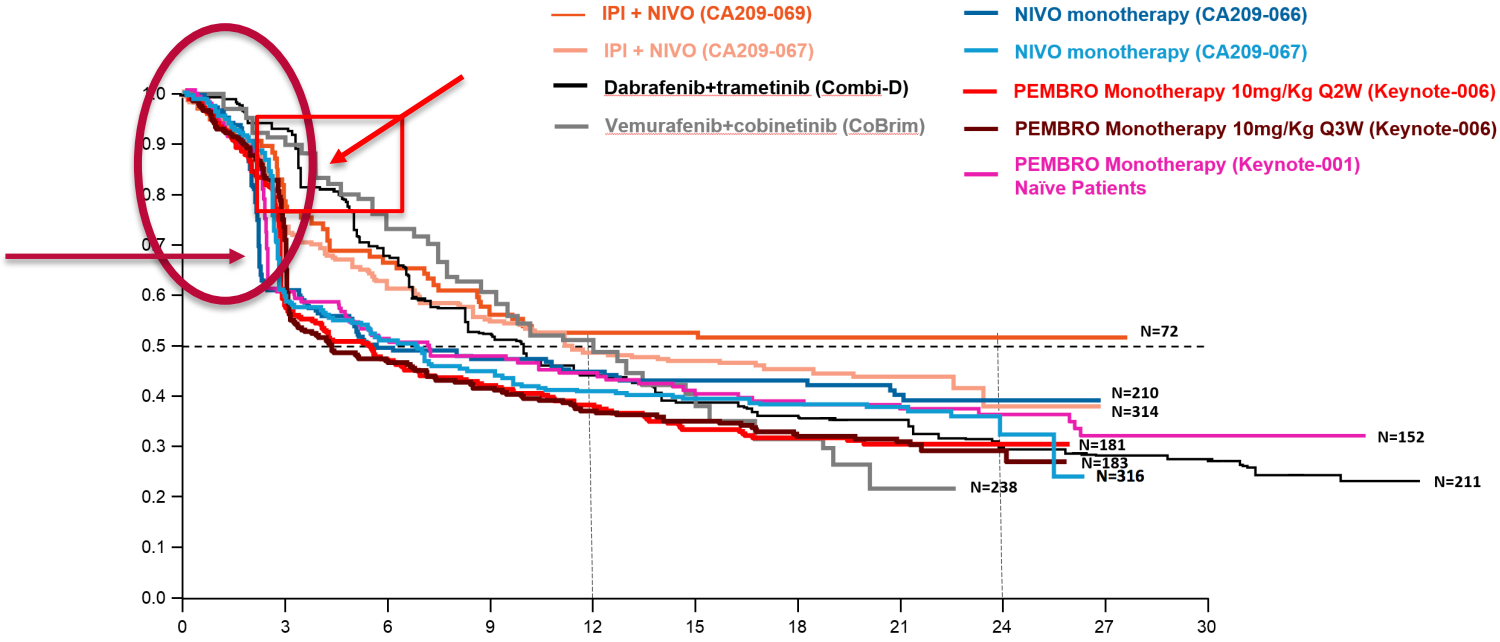
Checkpoint Blockers & Agonists	Small Molecules	Vascular Targets	Traditional Rx XRT, ChemoRx, Target Rx	Cytokines	Intratumor	Cellular & Vaccines
Combination	Epigenetic	Vascular "Zip Code"	Immunogenic death	Inflammation	△ TME	TAg presentation
Sequence	IO Pathway targets	Normalization	IO impacts	Regulation	Abscopal	Starting Product
Resistance	△ TME	△ TME	△ TME	Migration		Product Survival
PK/PD/Toxicity	PK/PD/Toxicity	PK/PD/Toxicity	TKI regulation of IO pathway	PK/PD/Toxicity		PK/PD/Toxicity
Non classical CPs Micorbiome Adrenergic R						

Future Directions: Defining and Overcoming Resistance

- Primary Resistance
- Secondary Resistance
- Resistance after treatment discontinuation

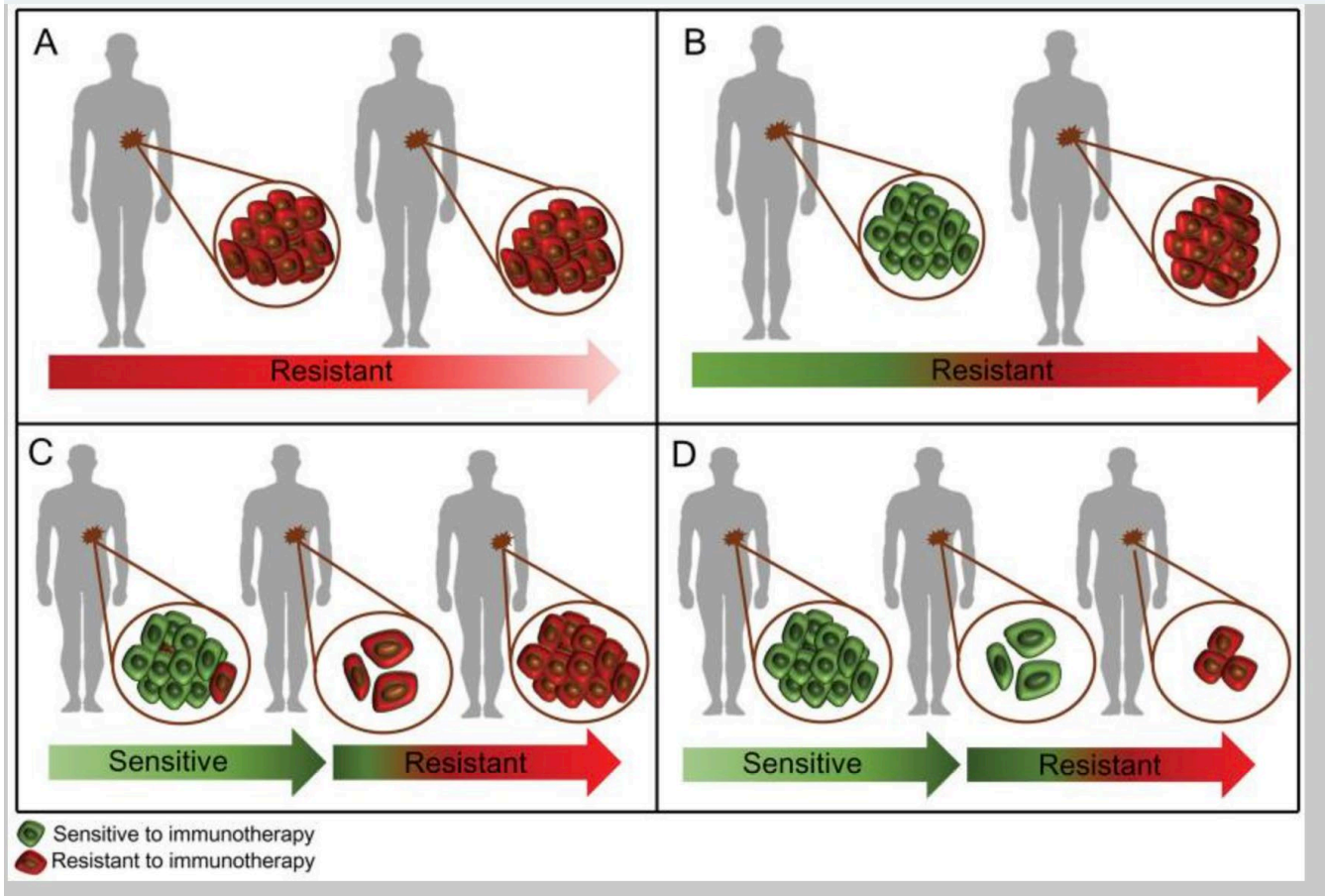
Primary vs. Secondary Resistance
Clinical Data observations

PFS Landmark analysis of the most important studies in advanced melanoma



Resistance Mechanisms

Sharma et al
2017 Cell



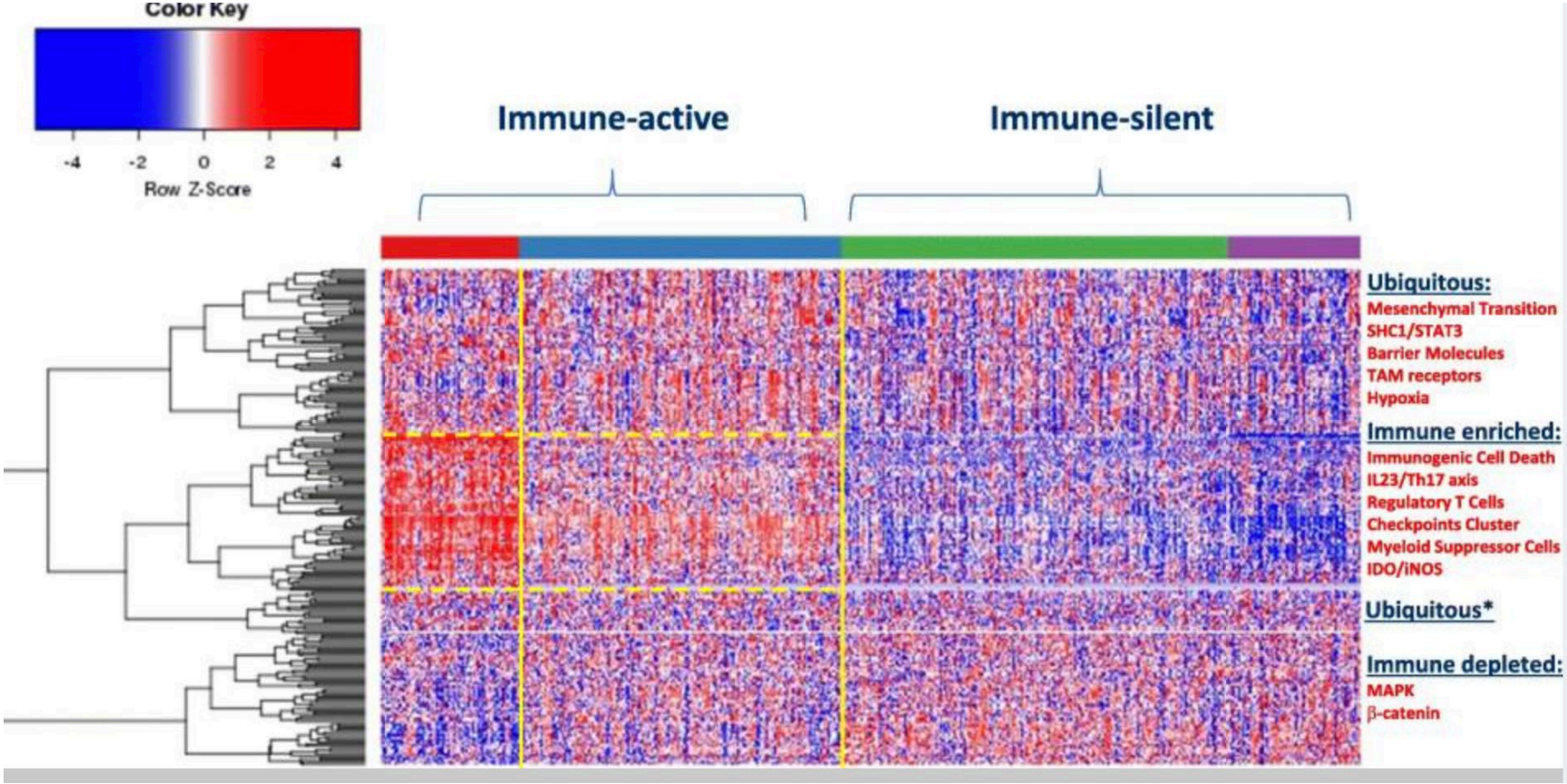
A: No immune response

B: Immune response
No Clinical Response

C: Resistant clones

D: Acquired immune
resistance

Turan et al
JITC 2018



Integrated Approach to Overcome Resistance

Clinical Data for the New Immune Therapies

The Median is not the Message: Stephen Jay Gould 1991

When diagnosed with abdominal mesothelioma he read that the 'median mortality' was eight months and concluded that most people would read such a statement as 'I will probably be dead in eight months.'

Dr. Gould's observation:
Firstly that, biologically, it is variation that is the hard reality rather than imperfect measures for a central tendency.

Secondly, that even with knowledge of prognostic features it is often difficult at diagnosis to know whether any individual is going to be to the left or right of the median. As many curves are right-skewed some patients will survive a long time, which was the case with Gould who died of another cause some years later.

Contact Marc S. Ernstoff, MD: marc.ernstoff@nih.gov

www.cancer.gov

www.cancer.gov/espanol

Extra slides

PK Interferon by route

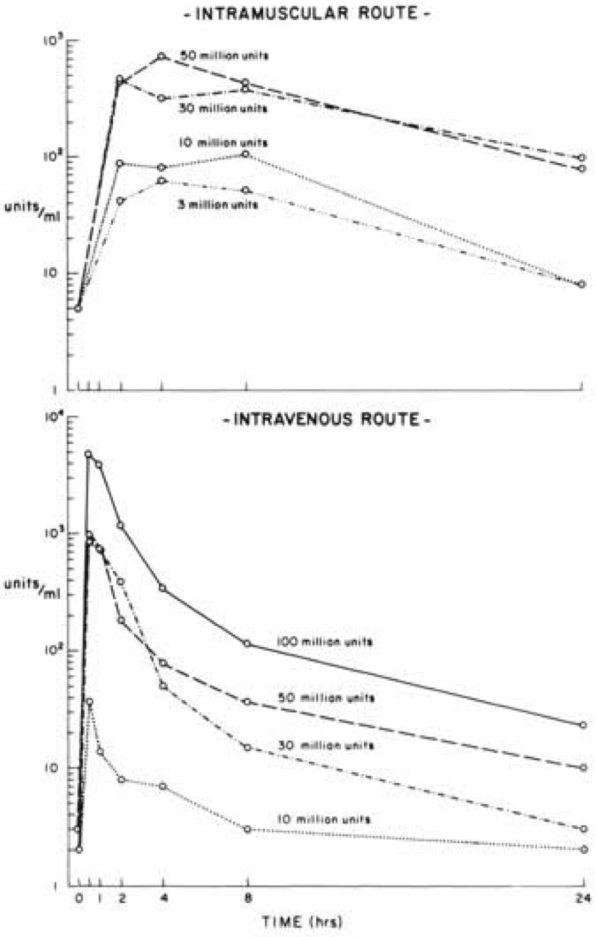
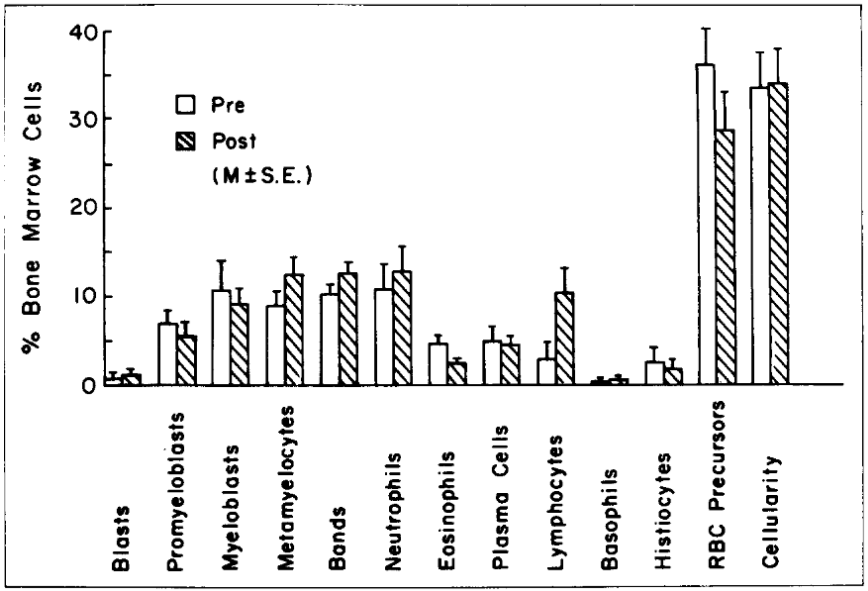


Figure 2. Pharmacokinetics of interferon alpha-2 according to route of administration and dosage in 33 patients. Serum interferon levels were measured by radioimmunoassay.

Kirkwood, Ernstoff et al 1985

PD of Interferon



Ernstoff et al 1984

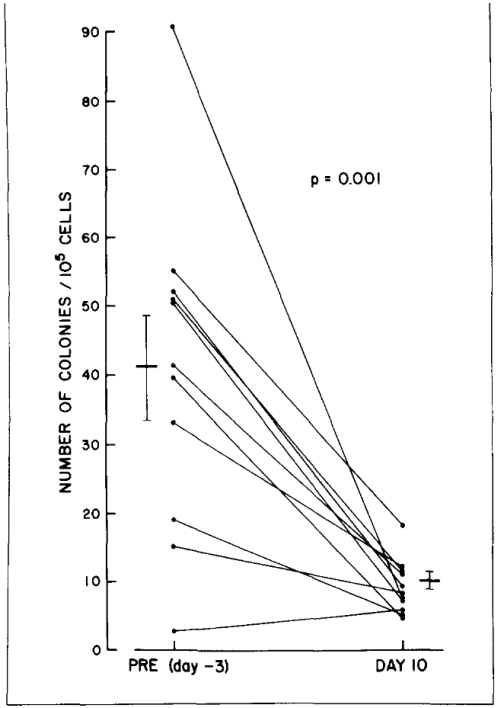
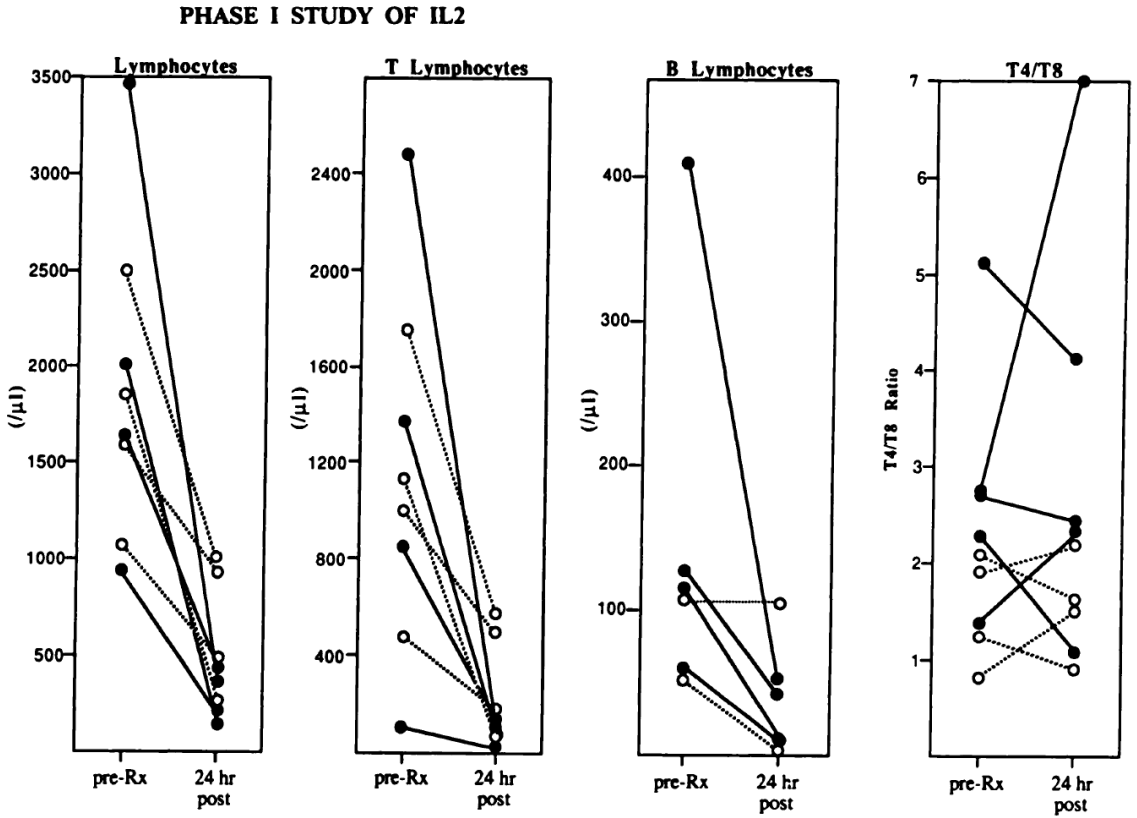


Figure 2. *Human bone marrow colony-forming granulocyte-macrophage cell assay for each patient and as mean ± SE (n = 11).*

Ernstoff et al 1985

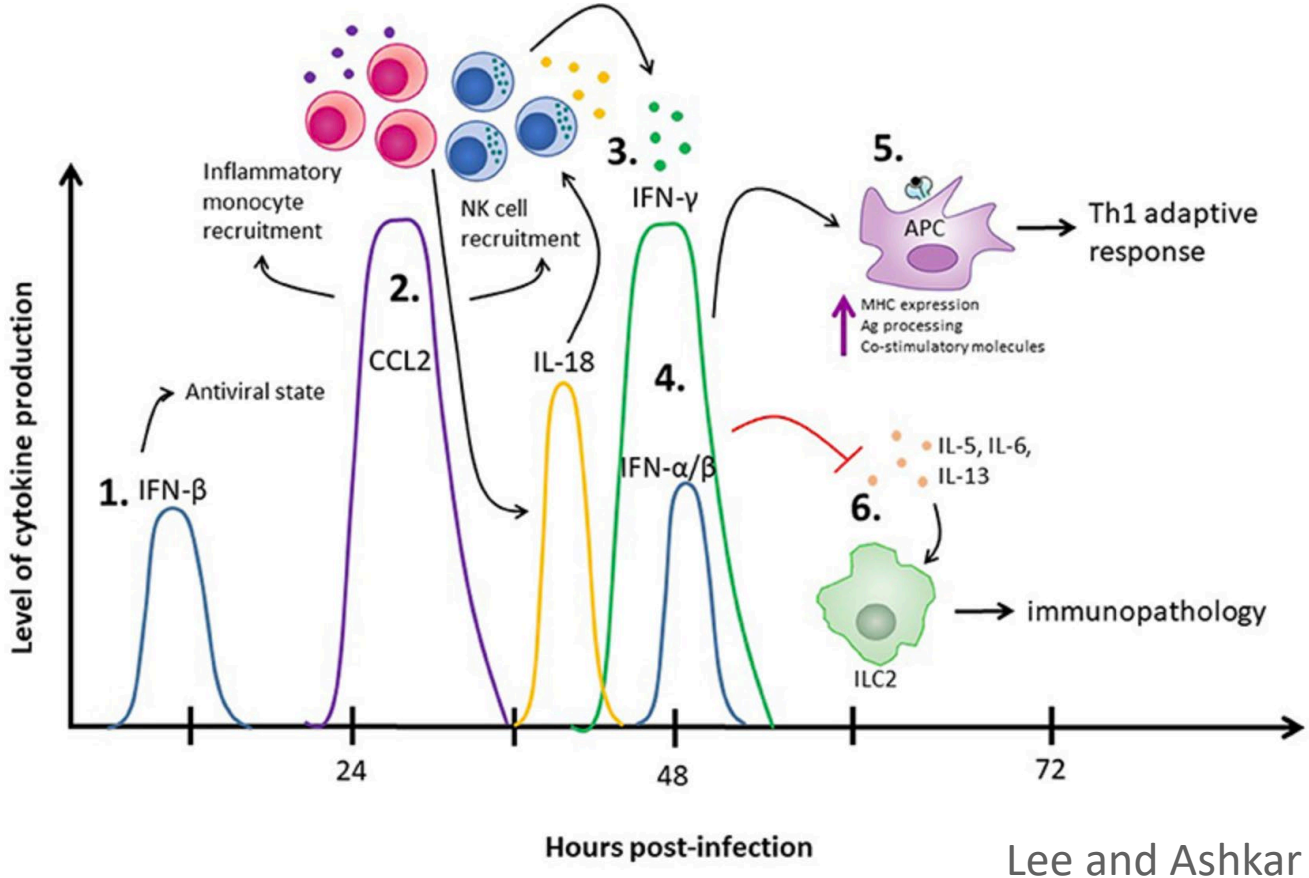
PD rHIL-2

Fig. 1. Changes in lymphocyte number after 24-h IL2 infusions. The absolute lymphocyte count was determined for patients pre-, and 24 h post-, IL2 treatment (*Rx*). The absolute number of lymphocytes staining with OKT3 (T-lymphocytes) or Leu 12 (B-lymphocytes) is shown, as well as the OKT_4:OKT_8 ratio. ○, 1×10^6 units of IL2 over 24 h; ●, 10×10^6 units of IL2 over 24 h.



Thompson JA et al 1987

IFNs acute phases



Lee and Ashkar 2018

Future Directions for Checkpoint Inhibition:
Small Molecules

Therapeutic monoclonal antibodies versus small molecule therapies

Monoclonal antibodies	Small molecule therapies
Larger (~150kD); mainly extracellular	Smaller (<1 kD); able to enter cells and cross blood-brain barrier
Target-specific	Less specific
Parenteral administration	Oral administration possible
Longer dosing interval (half-life: days to weeks)	Shorter dosing interval (half-life: hours)
Not eliminated via hepatic, renal or biliary routes	Elimination via hepatic, renal and/or biliary routes
Lower risk of drug-drug interactions	Drug-drug interactions possible