IMMUNOTHERAPY: A NEW FRONTIER IN MEDICAL ONCOLOGY

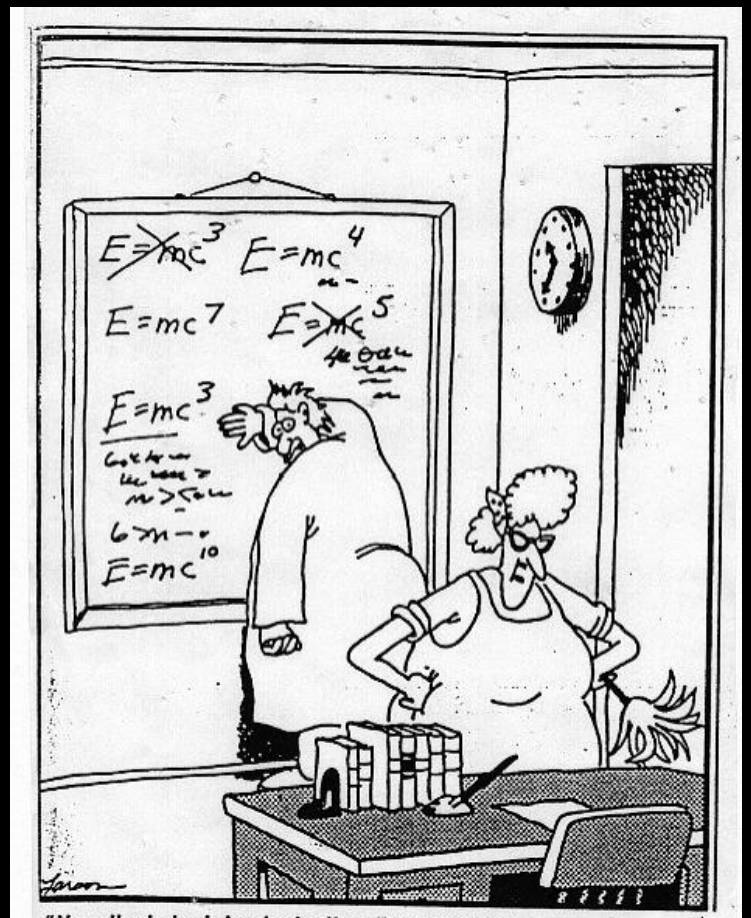
ACP Chapter Meeting

October 10, 2019

Jeremy M. Deutsch, MD

OBJECTIVES

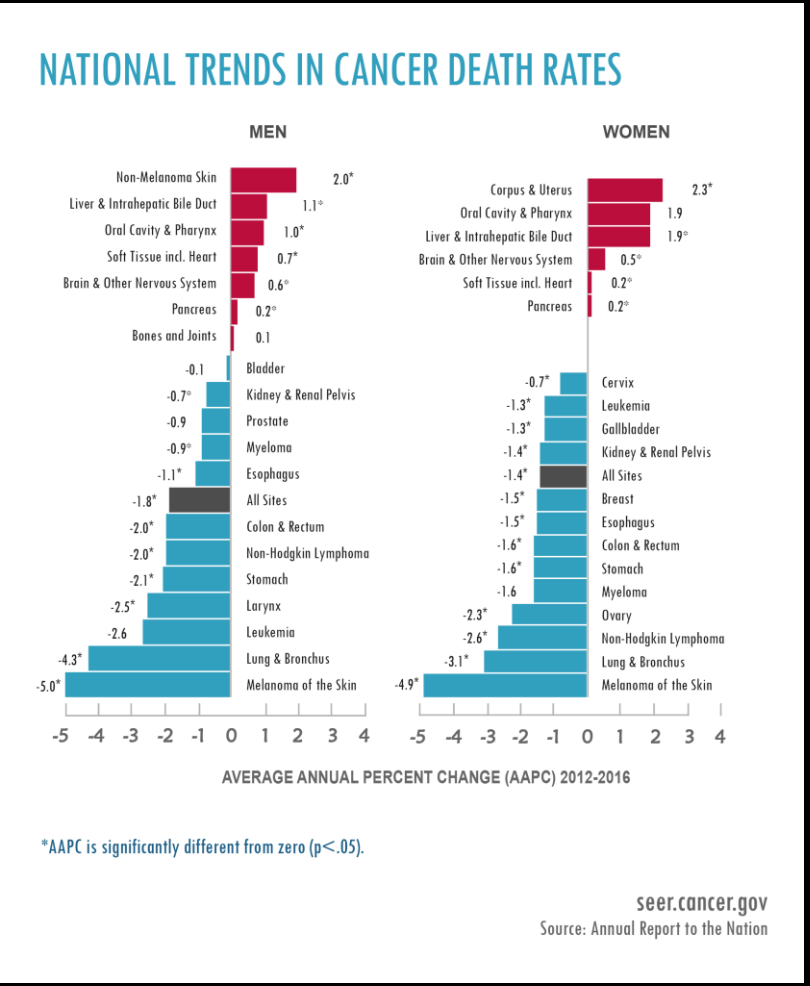
- Historical Perspectives
- Classical Approaches
- Paradigm Shifts
- Small Molecule Inhibitors
- Immunotherapy: Benefits & Risks
- “Gene” Therapy



"Now that desk looks better. Everything's squared away, yessir, squaaaaaared away."

BACKGROUND

- Why is this topic important?
  - In 2019, an estimated 1,762,450 new cases of cancer will be diagnosed in the United States and 606,880 people will die from the disease
  - Approximately 39.3% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2012-2016 data)



NCI. www.cancer.gov; www.seer.cancer.gov. 2013-2019.

BACKGROUND

- But, how are we doing?
  - In the United States, the overall cancer death rate has declined since the early 1990s
    - 1.8% per year among men from 1999 to 2016
    - 1.4% per year among women from 2002 to 2016
    - 1.4% per year among children ages 0–19 from 2009 to 2013
  - This has led to an increase in survivors of cancer:
    - The number of people living beyond a cancer diagnosis reached nearly 15.4 million in 2016 and is expected to rise to almost 19 million by 2024.

NCI. www.cancer.gov; www.seer.cancer.gov. 2013-2017.

ORIGINS

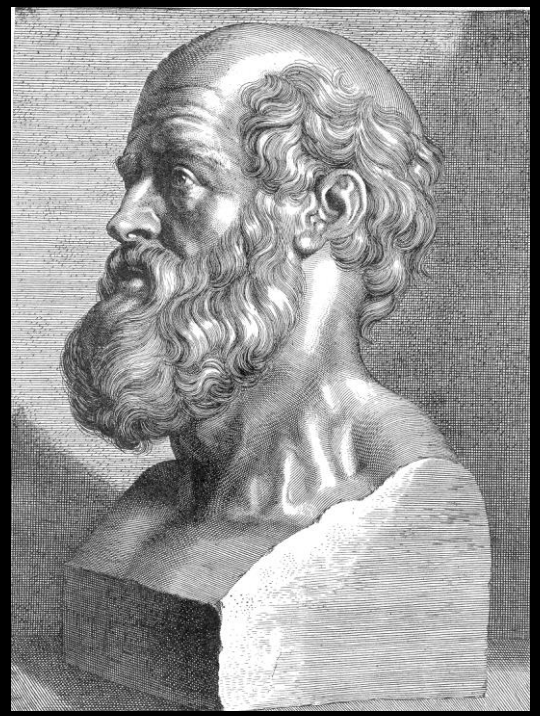
- Dr. Rudolf Virchow entered medicine in the 1840s
- Sought to provide more unifying theories of disease instead of the traditional descriptors:
  - Miasmas, hysterias, bad / foul humors, neuroses

- Cellular theory
  - Hypertrophy
  - Hyperplasia
  - … *Neoplasia*

Mukherjee S. The Emperor of All Maladies. Simon & Schuster. 2010.

HEMATOLOGY HISTORY

- *THE FOUR HUMORS*

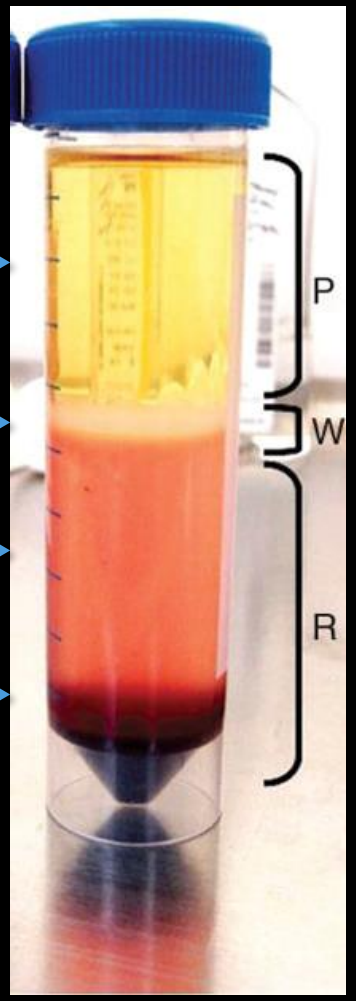


Yellow Bile
SERUM

Phlegm
WBC

Blood
OXYGENATED RBC

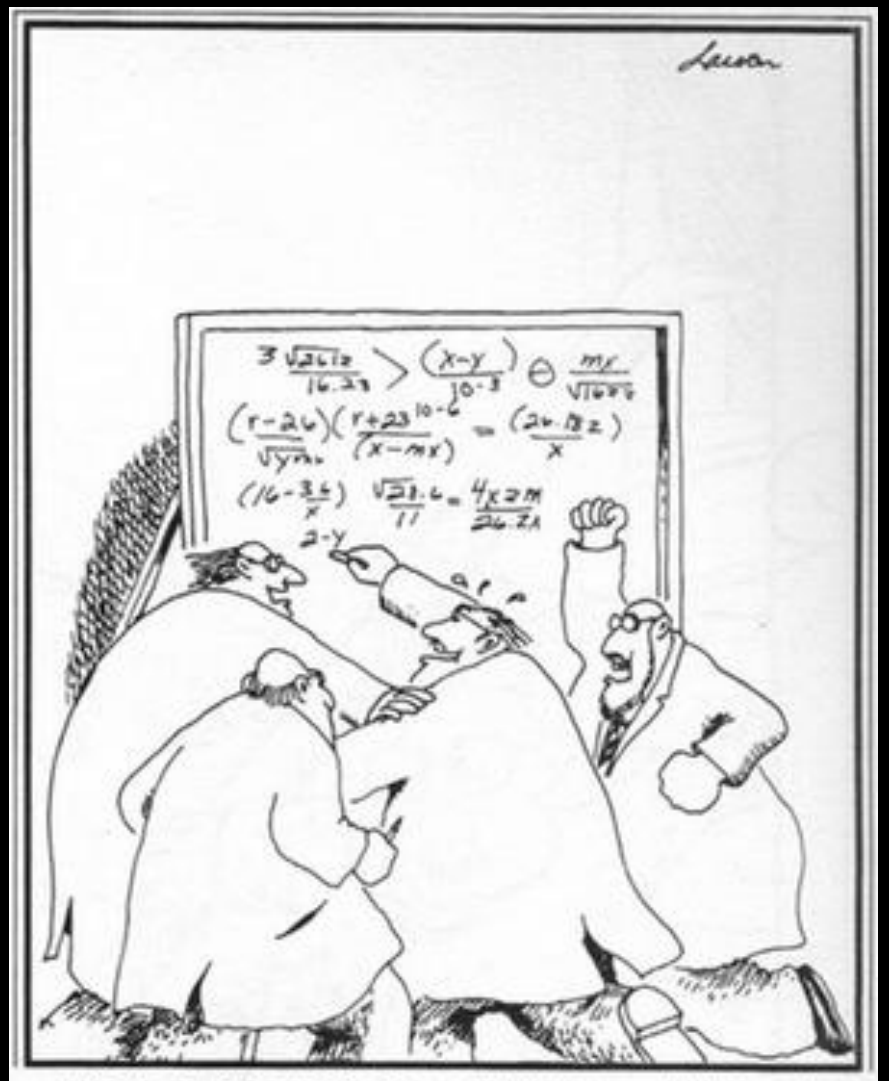
Black Bile
DEOXYGENATED RBC



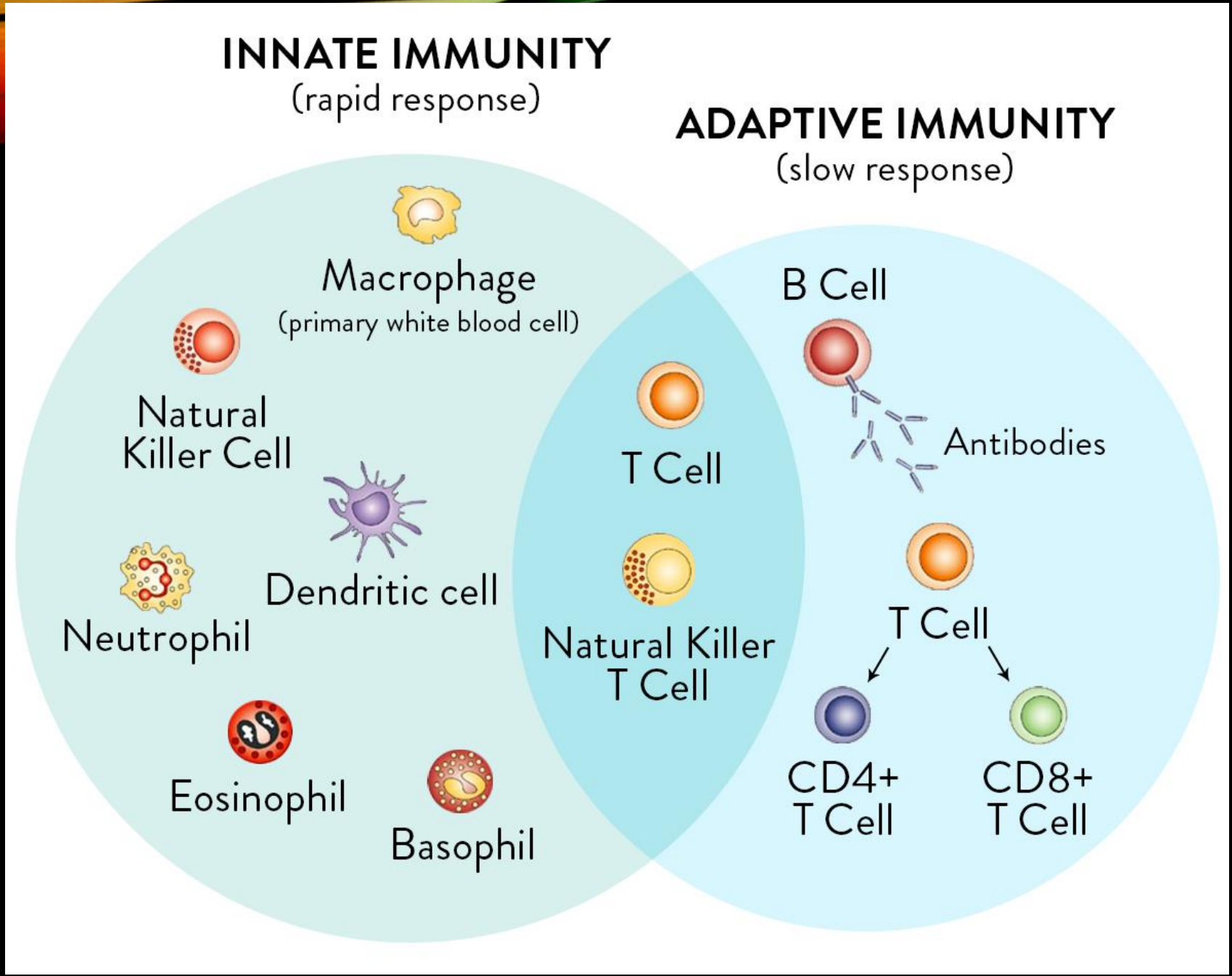
Teferri, A. Leukemia (2008) 22, 3-13.

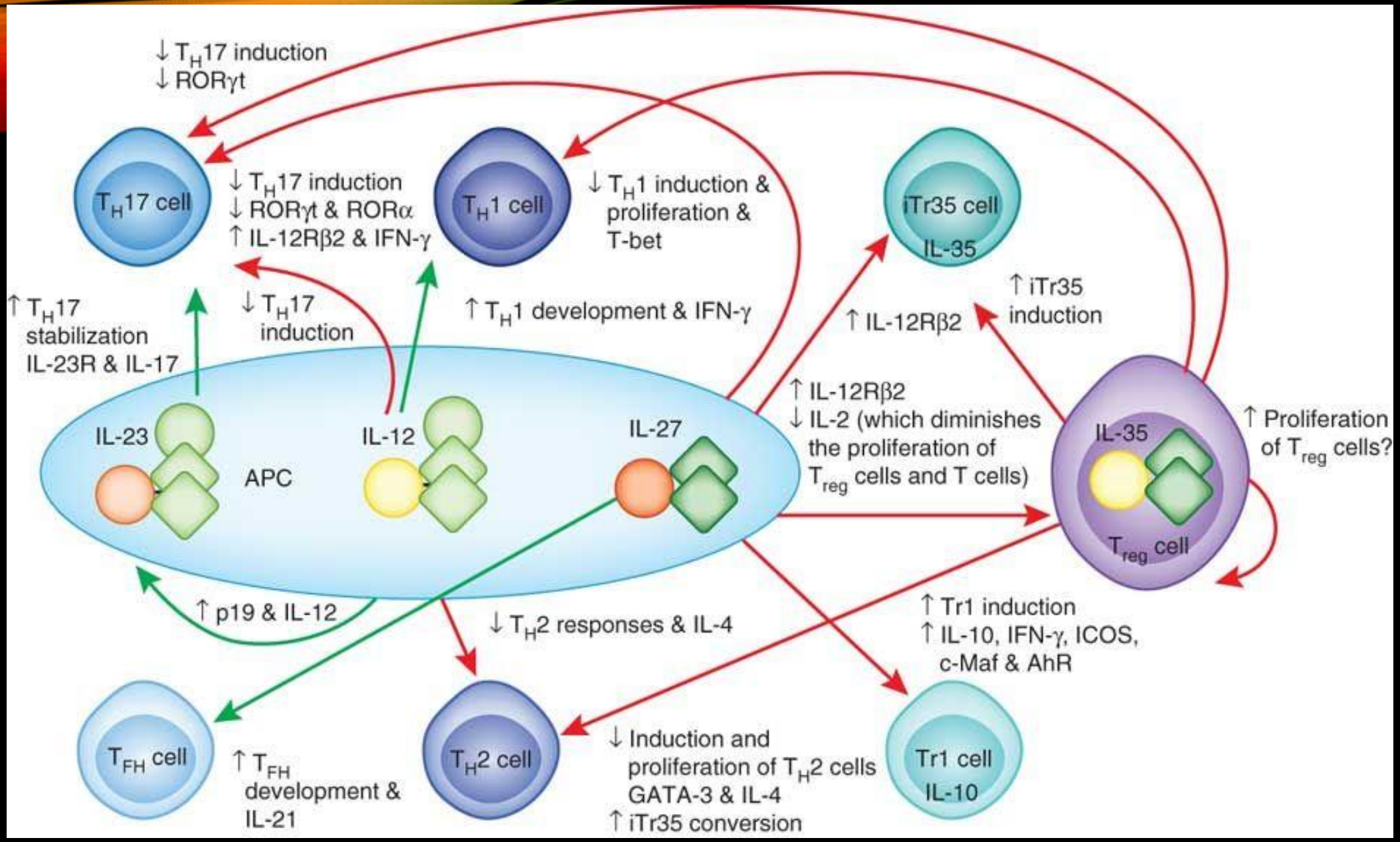
IMMUNOLOGY PRIMER

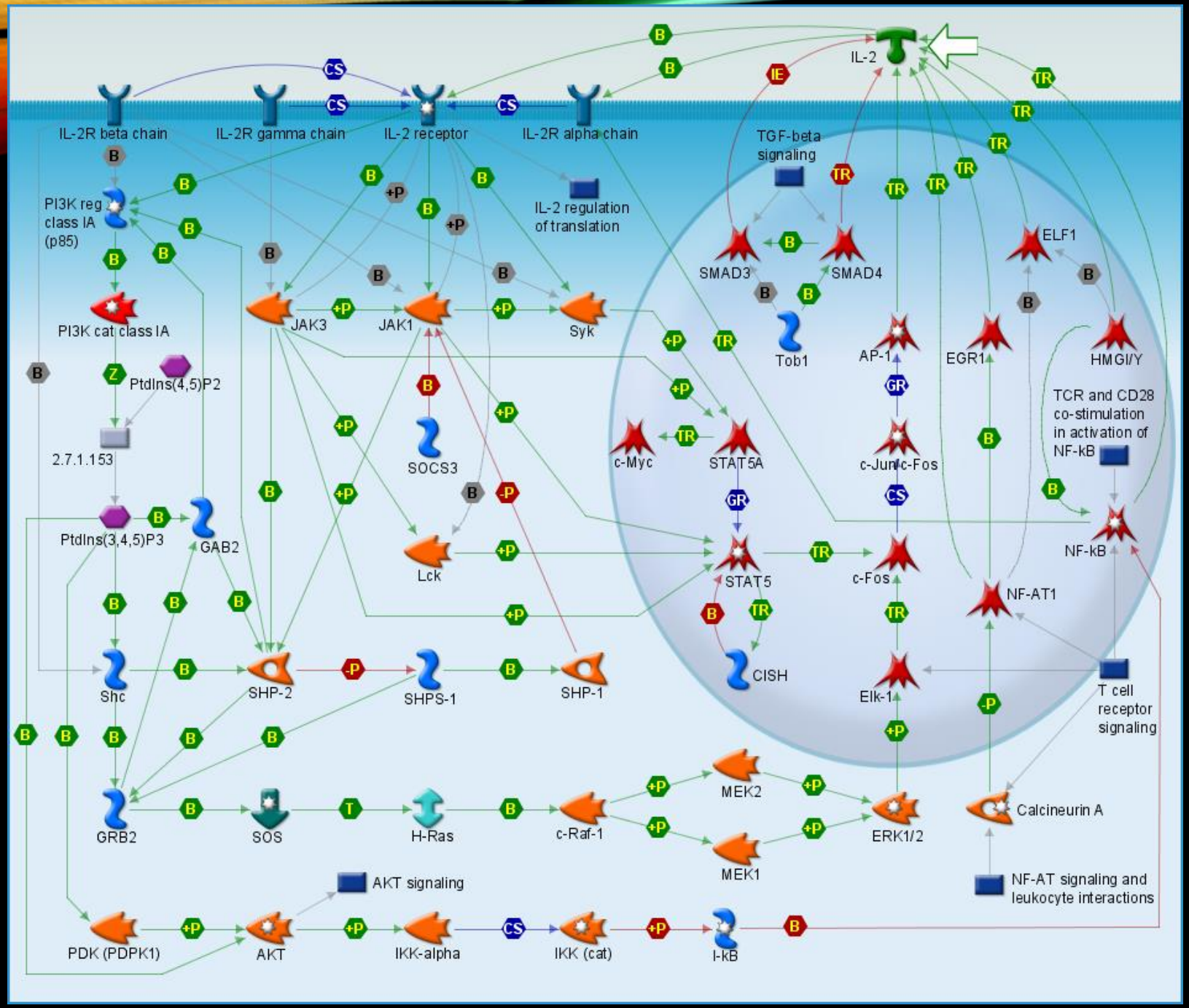
- (I'm sorry… really)



"Go for it, Sidney! You've got it! You've got it! Good hands! Don't choke!"


INNATE IMMUNITY
(rapid response)
ADAPTIVE IMMUNITY
(slow response)
Macrophage
(primary white blood cell)
Natural Killer Cell
Dendritic cell
Neutrophil
Eosinophil
Basophil
T Cell
Natural Killer T Cell
B Cell
Antibodies
T Cell
CD4+ T Cell
CD8+ T Cell


↓ T_H17 induction
↓ RORγt
T_H17 cell
↓ T_H17 induction
↓ RORγt & RORα
↑ IL-12Rβ2 & IFN-γ
T_H1 cell
↓ T_H1 induction & proliferation & T-bet
iTr35 cell
IL-35
↑ T_H17 stabilization IL-23R & IL-17
↓ T_H17 induction
↑ T_H1 development & IFN-γ
↑ IL-12Rβ2
↑ iTr35 induction
↑ IL-12Rβ2
↓ IL-2 (which diminishes the proliferation of T_{reg} cells and T cells)
IL-23
APC
IL-12
IL-27
IL-35
T_{reg} cell
↑ Proliferation of T_{reg} cells?
↑ p19 & IL-12
↓ T_H2 responses & IL-4
↑ Tr1 induction
↑ IL-10, IFN-γ, ICOS, c-Maf & AhR
T_{FH} cell
↑ T_{FH} development & IL-21
T_H2 cell
↓ Induction and proliferation of T_H2 cells GATA-3 & IL-4
↑ iTr35 conversion
Tr1 cell
IL-10

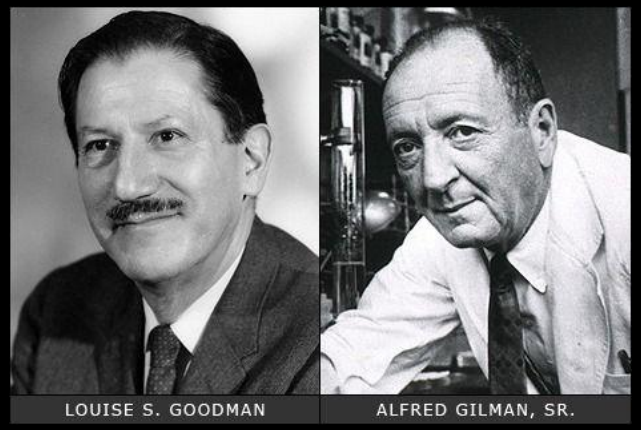

IL-2
IL-2R beta chain
IL-2R gamma chain
IL-2 receptor
IL-2R alpha chain
TGF-beta signaling
IL-2 regulation of translation
PI3K reg class IA (p85)
PI3K cat class IA
PtdIns(4,5)P2
2.7.1.153
PtdIns(3,4,5)P3
GAB2
JAK3
JAK1
Syk
SOCS3
Lck
SMAD3
SMAD4
Tob1
AP-1
EGR1
ELF1
HMGI/Y
TCR and CD28 co-stimulation in activation of NF-kB
c-Myc
STAT5A
c-Jun/c-Fos
STAT5
c-Fos
NF-kB
NF-AT1
CISH
Elk-1
T cell receptor signaling
Shc
SHP-2
SHPS-1
SHP-1
GRB2
SOS
H-Ras
c-Raf-1
MEK2
MEK1
ERK1/2
Calcineurin A
AKT signaling
NF-AT signaling and leukocyte interactions
PDK (PDPK1)
AKT
IKK-alpha
IKK (cat)
I-kB

CLASSICAL APPROACHES

Cytotoxic chemotherapies & Success Stories

BEGINNINGS OF CHEMOTHERAPY

- 1946: Goodman and Gillman
  - Mustine, nitrogen mustard, *SS John Harvey*
  - The first patient: lymphoma



- 1947: Sidney Farber
  - Pathologist turned investigator
  - Childhood leukemia
  - Aminopterin (precursor of methotrexate)

Goodman LS, et al. Nitrogen mustard therapy. JAMA. 132(3): 126-132.
Mukherjee S. The Emperor of All Maladies. Simon & Schuster. 2010.

DRUG DEVELOPMENT

- Progress has been met with more regulation, more controlled environments and stricter criteria for effectiveness
- NCI established in 1955
- Combination chemotherapy (ALL, 1965)
- Adjuvant therapy (Osteosarcoma, 1974)

Abeloff (2004). Clinical Oncology (3rd ed.). Churchill Livingston. pp. 408–413
Jaffe N, Frei E, III, Traggis D, Bishop Y. Adjuvant methotrexate and citrovorum factor treatment of osteogenic sarcoma. The New England Journal of Medicine. 1974;291(19):994–997.

CYTOTOXIC CHEMOTHERAPY

- Success stories have occurred in multiple tumor types:
  - Lymphoma (Hodgkin / Non-Hodgkin)
  - Testicular / Germ Cell Tumors
  - Childhood Leukemias
  - Adult Leukemias
- However:
  - Less successful in other histologies
  - Dose-response curve / AUC
  - Dose intensity
  - Adverse events

Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. J Natl Compr Canc Netw 2009; 7:99.

CANCER CHEMOTHERAPY

- Limitations
  - Toxicities
  - Mortality
  - Lack of response
  - Mutagenic abilities of malignancies

Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol 1986; 4:1162.

PARADIGM SHIFTS

THE "FOUR MINUTE MILE OF CANCER"

- Chronic Myelogenous Leukemia
- The Philadelphia Chromosome
- bcr/abl
- Dr. Brian Druker
- STI571 / Imatinib

Mukherjee S. The Emperor of All Maladies. Simon & Schuster. 2010.

THE "FOUR MINUTE MILE OF CANCER"

- Imatinib, unprecedented success
  - Palpable sensation in the field that *THE* breakthrough for all cancer types was on the horizon
  - Editorial by Bruce Chabner, 1999

- 'Perfect Inversion of the goals of cancer medicine'

Mukherjee S. The Emperor of All Maladies. Simon & Schuster. 2010.

SMALL MOLECULE INHIBITORS

- The bcr/abl payoff
- Vascular blockade
- BTK Inhibition
- CDK4/6 (Cell Cycle) Inhibition

- ***…and the side effects***

IMMUNOTHERAPY

Checks and Balances

IMMUNOTHERAPY

- Currently approved therapies:
  - Cytokines / Cytokine stimulation
  - CTLA-4 inhibitors
  - PD-1 inhibitors
  - PD-L1 inhibitors
  - CAR-T cell therapy (more in a bit)

MODULATING THE IMMUNE RESPONSE

- Harnessing the power and potential of the innate and adaptive immune system has long been a goal of cancer therapy
- The first documented use of immunotherapy in cancer therapy was in the late 19th century
  - Dr. W. Coley & 'Coley's toxin'
  - Injected a mixture of live (!) bacteria into sarcomas
  - Had some results (tumor regressions)
  - Mechanisms weren't understood
  - Patient deaths
  - Results weren't repeatable / reproducible

Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas: with a report of ten original cases. Am J Med Sci 1893; 105:487.

CYTOKINE STIMULATION

- High Dose IL-2
  - Renal cell carcinoma (kidney cancer)
  - Melanoma (skin cancer)
- Whipping up an 'immunologic storm'…
  - … and hoping to win the lottery
- Proof of concept
- Toxicities: High fevers, confusion, low blood pressures, heart failure, swelling

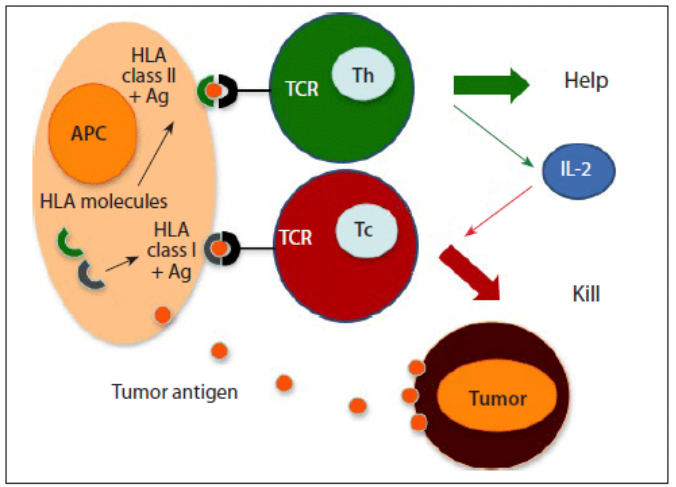
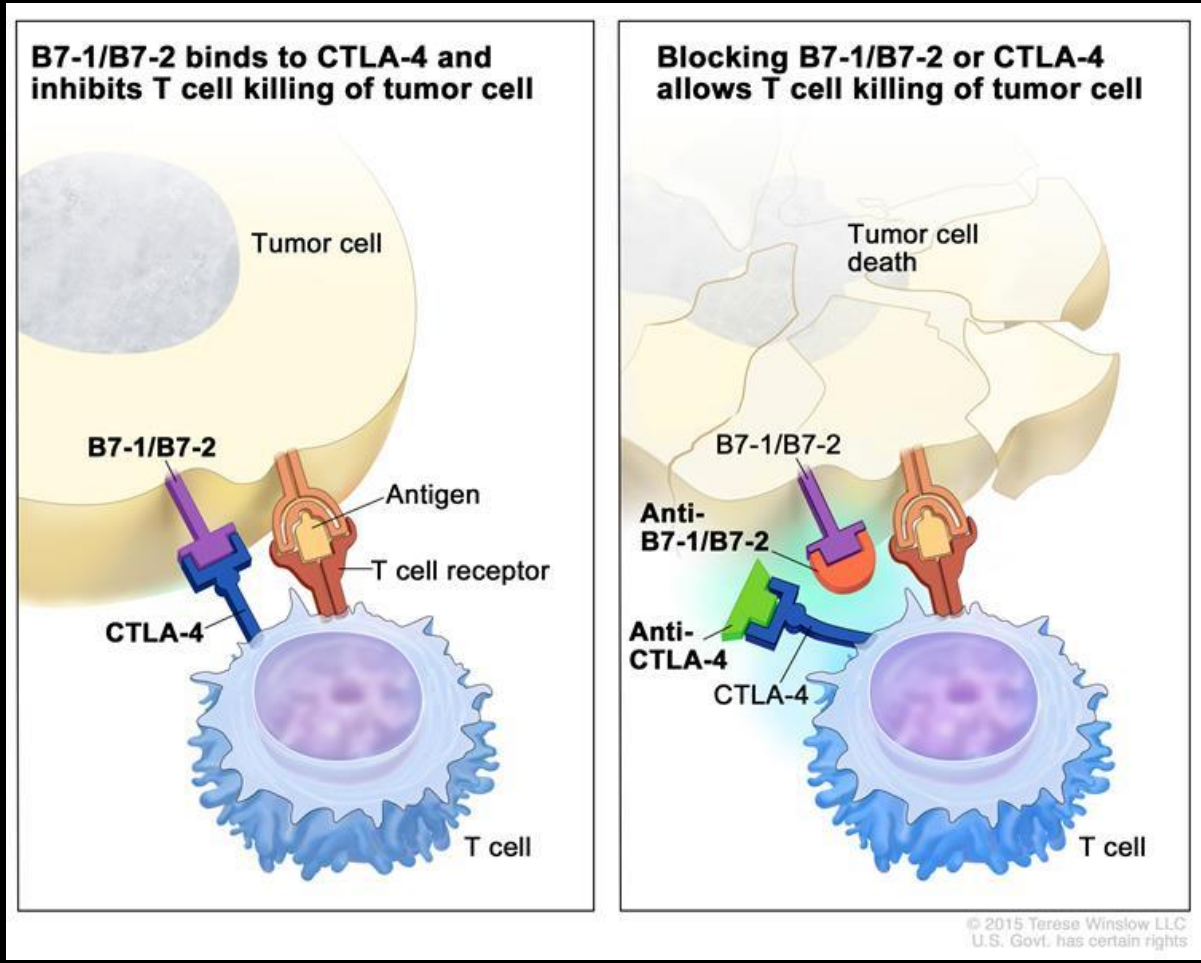


Figure A: Generation of Anti-Tumor Immune Response by T Lymphocytes—Ag = antigen; APC = antigen-presenting cell; HLA = human leukocyte antigen; IL-2 = interleukin 2; Tc = cytotoxic T cell; TCR = T cell receptor; Th = helper T cell.

Amin A, et al. High-Dose Interleukin-2: Is It Still Indicated for Melanoma and RCC in an Era of Targeted Therapies? Cancernetwork.com. 15 Jul 2013.

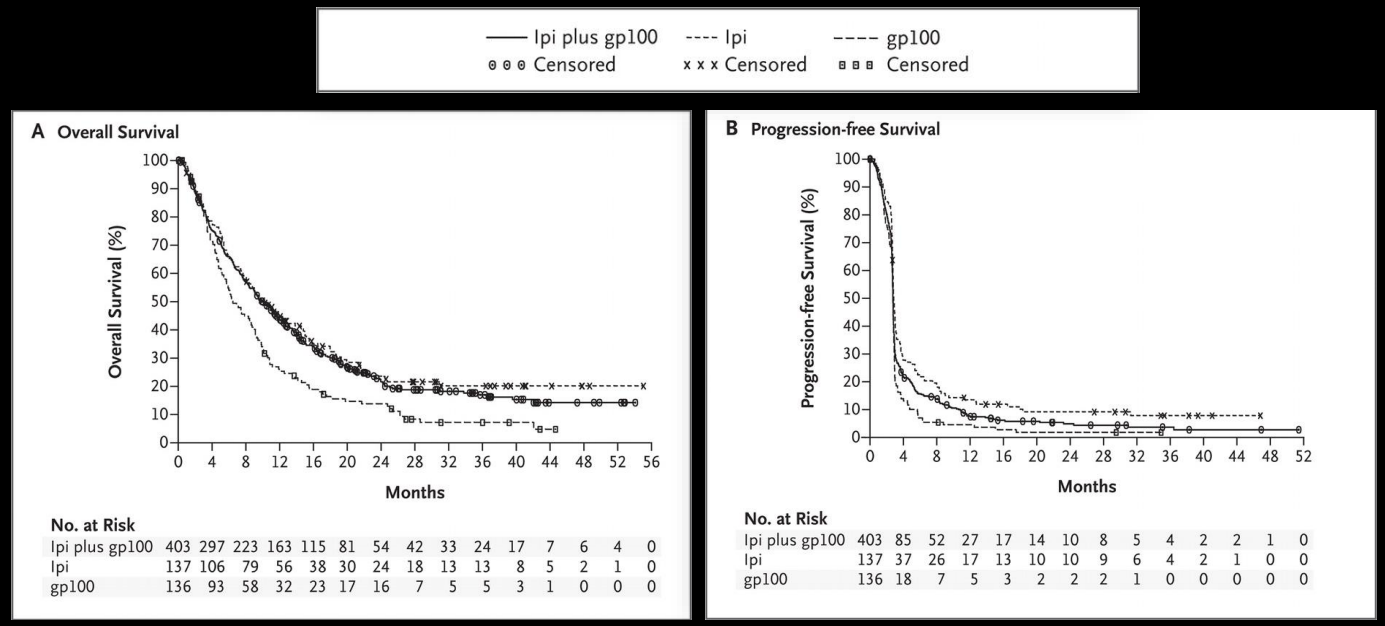
MODULATING THE IMMUNE RESPONSE: CTLA-4

- Ipilimumab: first in class
- An attempt at 'cleaner' immunotherapy
- Removal of the natural 'immunologic brakes'



MODULATING THE IMMUNE RESPONSE: CTLA-4

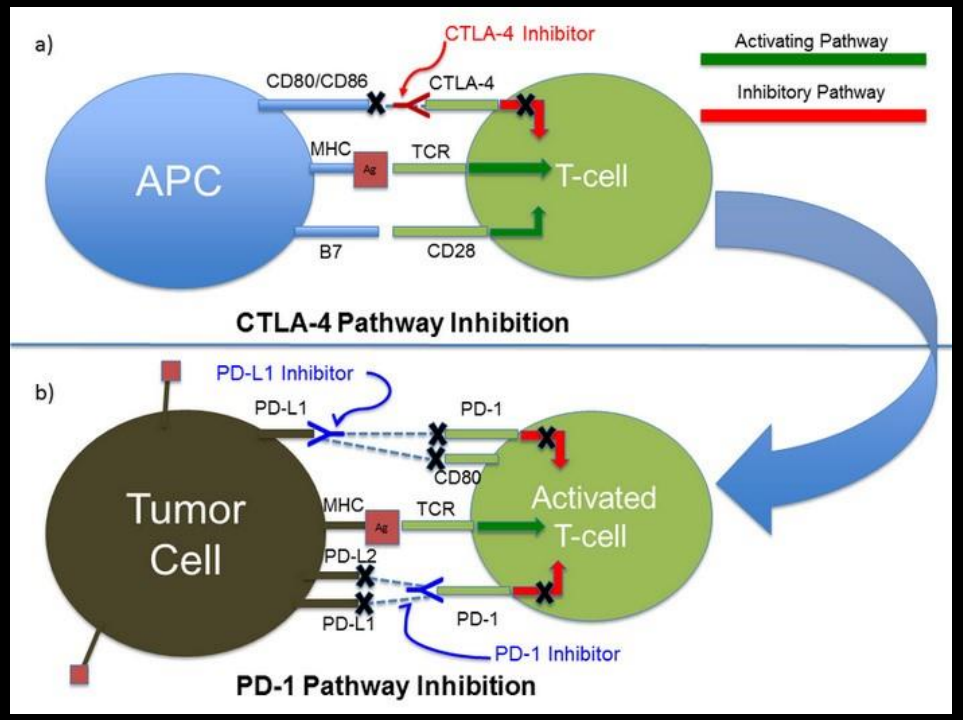
- Success in melanoma
- ‘Unprecedented numbers’; doubling the number of patients alive after 1 years (43%)



Hodi FS, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 2010; 363:711-723.

CHECKPOINT INHIBITION

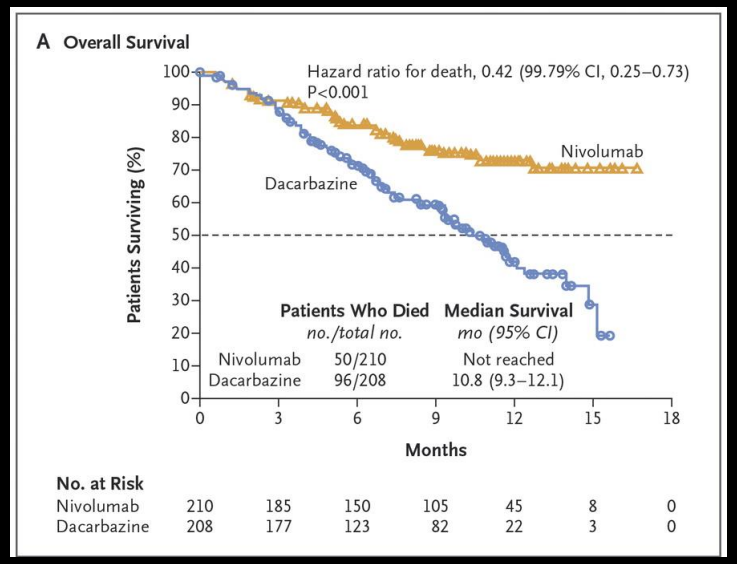
- Old concept in cancer therapy becomes new
- Immunologic manipulation
- PD-1, and PD-L1
- Mutational burden
- irAE: a whole new class

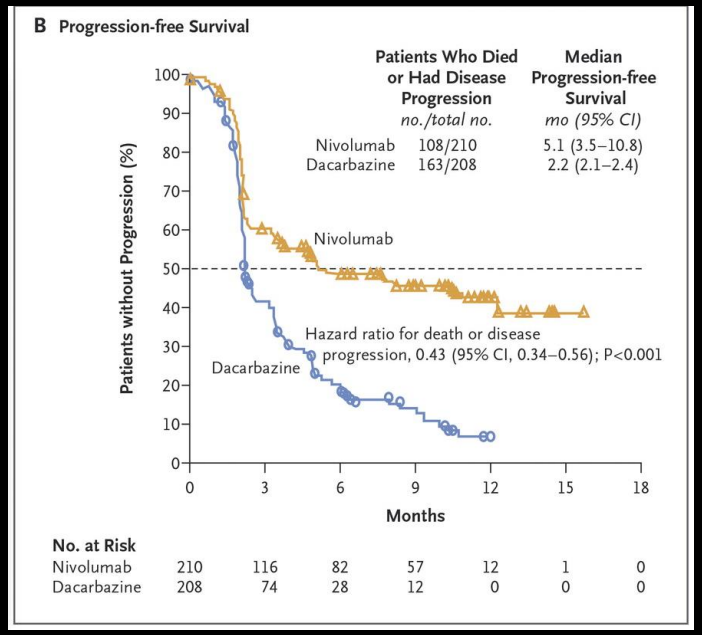


Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, Postow MA, Wolchok JD. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26(12):2375.

MODULATING THE IMMUNE RESPONSE: PD-1

- Success in melanoma
- ‘Unprecedented numbers’; doubling the number of patients alive after 1 years (73%)





Robert C, et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. N Engl J Med 2015; 372:320-330.

MODULATING THE IMMUNE RESPONSE: PD-1 / PD-L1

- With this success, research has expanded the scope of use of this concept:
  - Melanoma
  - Non-small cell lung cancer
  - Small cell lung cancer
  - Hodgkin Lymphoma
  - Kidney cancer
  - Bladder cancer
  - Colorectal cancer
  - Merkel cell carcinoma
  - Gastric cancer
  - …and more to come

IMMUNE RELATED ADVERSE EVENTS (IRAE)

- As the immune system is stimulated to act, an intentional expansion of the reach and volume of the immune system is anticipated
- At times, this is extraordinarily smooth in delivery with minimal side effects
- At other times, however…

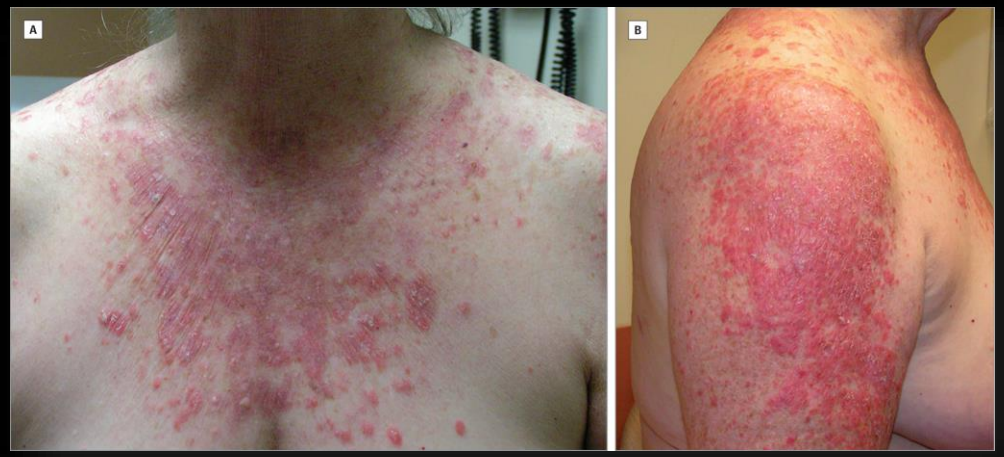
IRAE: SYSTEMIC

- **Fatigue**
  - Occurs in 16-24% of PD-1/PD-L1 treated patients (All grades)
  - Can be up to 40% of CTLA-4-I treated patients
  - Generally mild

- **Infusion-related reactions**
  - Mild reactions (itching, etc) occurs in 25% of patients
  - Life threatening reactions (anaphylaxis) is quite rare (<2%) across the classes

Naidoo J, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26(12):2375. Epub 2015 Sep 14

IRAE: DERMATOLOGIC



- **Dermatologic**
  - Most common toxicity in this class of medications
  - Usually the earliest toxicity (~3 weeks)
  - Highly variable (can range from mild rash to vitiligo to alopecia to Stevens-Johnsons Syndrome)

  - Management is generally steroid based: topical / oral / systemic depending on severity of rash, duration of rash, necessity of continuation of the medication

*Brahmer JR, et al. **Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline.** J Clin Oncol. 2018;36(17):1714. Epub 2018 Feb 14.*

IRAE: GASTROINTESTINAL

- **Colitis & Diarrhea**
  - Average time to onset is ~6 weeks
  - With ipilimumab, colitis can occur in 30% of cases; with 10% of those being severe (>7 stools per day)
  - THIS DIARRHEA CAN BE LIFE THREATENING
  - The earlier the recognition (and treatment initiation), the better the outcome
  - Colitis occurs in only 1-2% of cases with PD-1 / PD-L1 inhibitors
  - Management: 1) Hydration, 2) High dose corticosteroids, 3) Infliximab

Weber JS, et al. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer. 2013 May;119(9):1675-82. Epub 2013 Feb 7.

IRAE: HEPATIC

- **Hepatotoxicity**
  - Usually manifests as simple elevations of AST / ALT (and sometimes bilirubin)
  - Generally, is pretty rare:
    - 10% for ipilimumab
    - <5% for PD-1 inhibitors
    - 20% for ipilimumab + nivolumab

  - Management:
    - Generally, these are asymptomatic situations that can be either simply be monitored or treated with corticosteroids
    - Some case literature using MMF for refractory patients

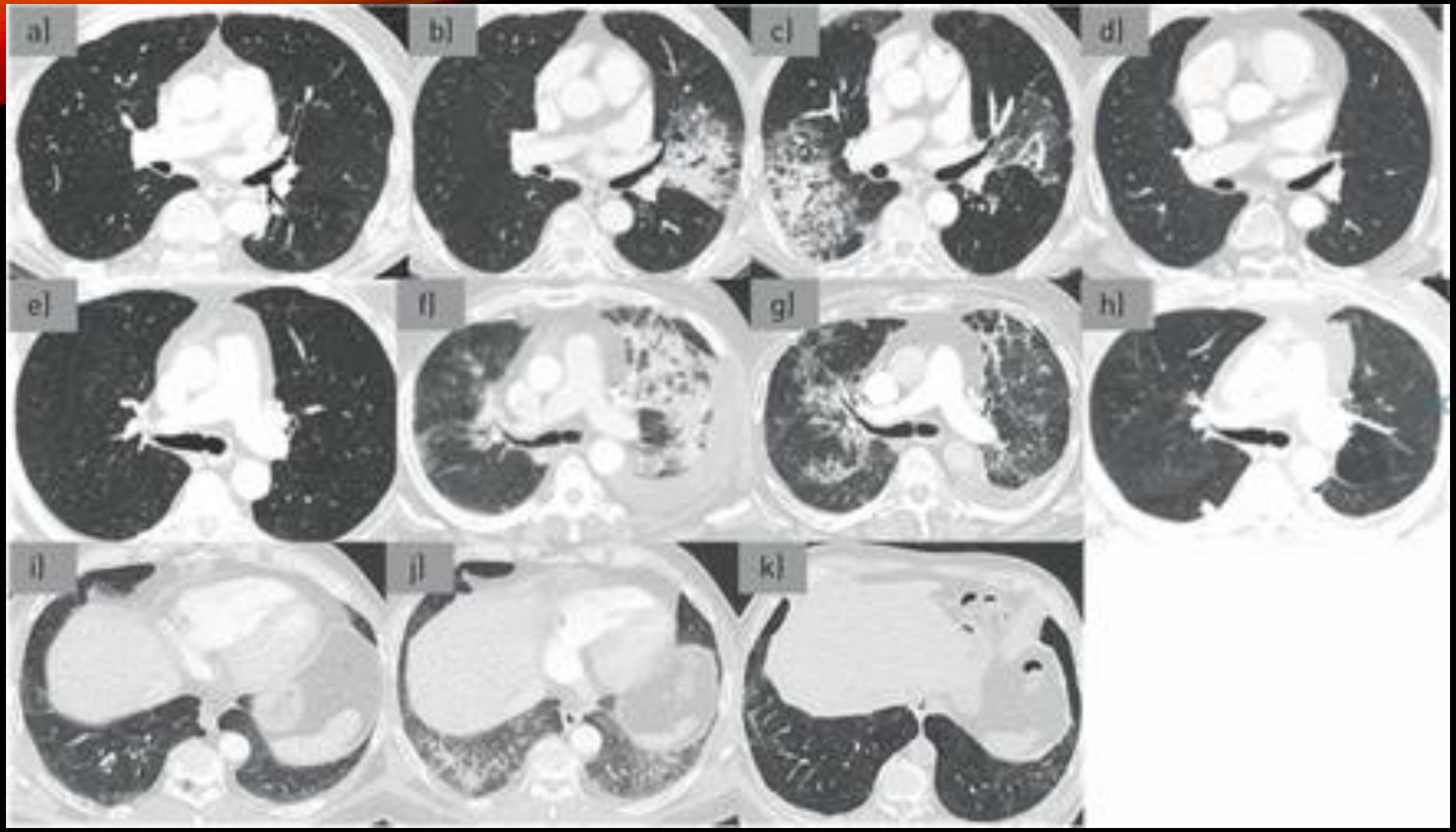
Brahmer JR, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714. Epub 2018 Feb 14.

IRAE: LUNG

- **Pneumonitis**
  - Average time to onset is about ~ 3 months into therapy
  - THIS SITUATION CAN BE LIFE THREATENING
  - Occurs in 3-10% of patients
  - More prominent in patients who have underlying interstitial lung disease or who have had chest radiation in the past (radiation recall)
  - Generally presents as acute hypoxic respiratory failure with diffuse infitrates

  - Management:
    - Corticosteroids with long associated taper
    - If steroids do not work: infliximab, cyclophosphamide

Brahmer JR, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714. Epub 2018 Feb 14.


a)
b)
c)
d)
e)
f)
g)
h)
i)
j)
k)

IRAE: ENDOCRIOPATHIES

- **Autoimmune thyroid disease**
  - Hyperthyroidism
  - Hypothyroidism
- **Hypophysitis**
- **Adrenal insufficiency**
- **Acute onset Type 1 Diabetes**

Brahmer JR, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714. Epub 2018 Feb 14.

IRAE: OTHERS

- Nephritis
- Pancreatitis
- Guillain-Barre Syndrome
- Myocarditis
- Acquired Hemophilia
- Conjunctivitis / Uveitis / Episcleritis
- Arthritis

CAR-T “GENE” THERAPY

CAR-T CONCEPTS

- Chimeric Antigen Receptors (CAR) are synthetic, engineered receptors that are made in a laboratory

- The idea behind this approach is to essentially synthesize two approaches to cancer
  - Monoclonal (specific) antibodies
  - T-cell therapy (immunotherapy)

CAR-T CONCEPTS

- This is a process that is heavy on biomedical / biochemical engineering

- Steps:
  - 1) Collect T-cells (blood draw) from the patient (specific to each & every patient)

  - 2) In a lab, the T-cells are exposed to an inactivated virus in order to convince / train them to express an engineered receptor on its surface (this receptor doesn't exist in nature)

  - 3) T-cells are 'expanded' (grown) in the lab to number in the millions

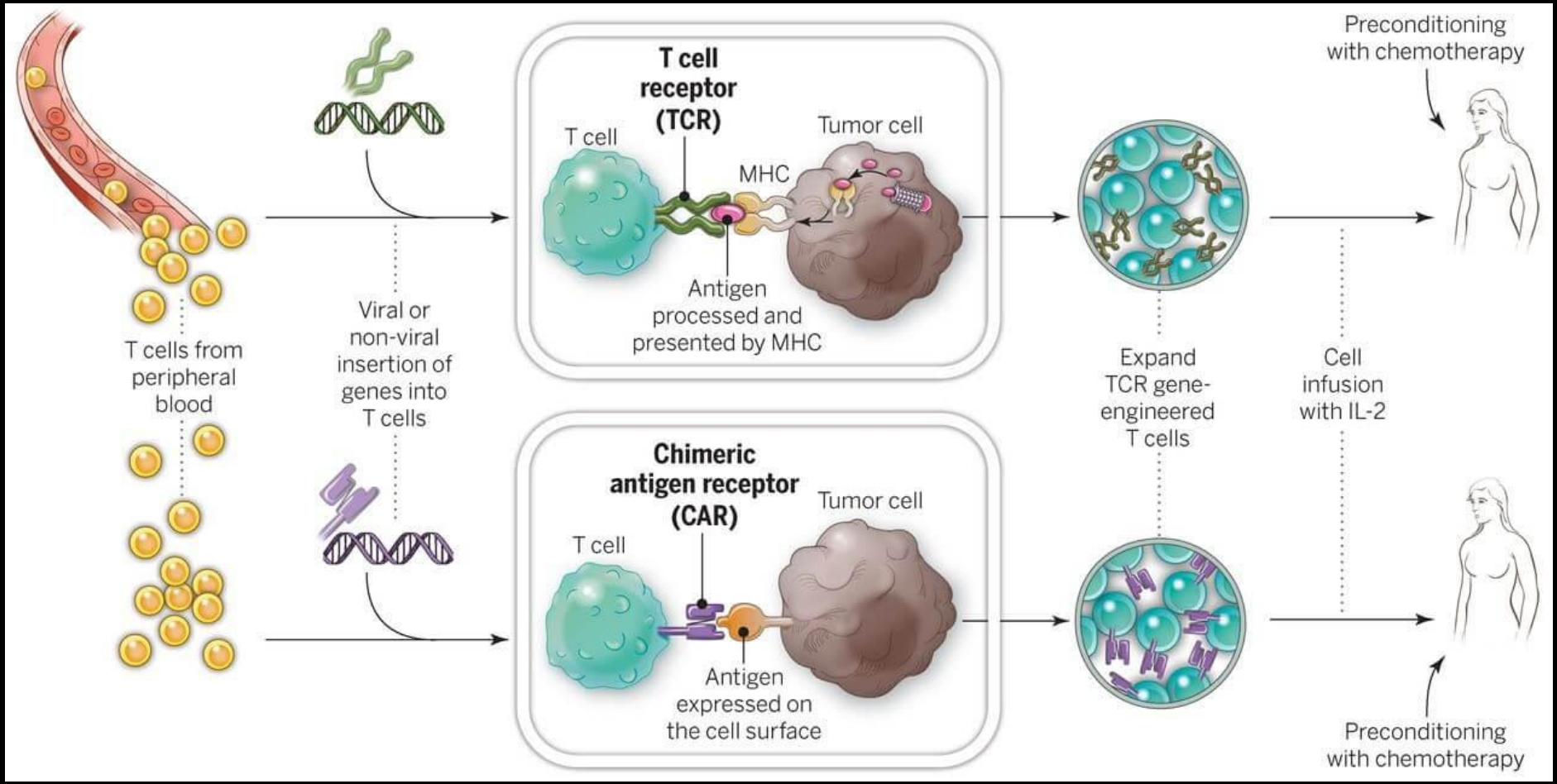
NCI. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. 31 Aug 2017.

CAR-T CONCEPTS

- Steps (continued):
  - 4) Patient receives dosing of chemotherapy to kill their existing lymphocytes
  - 5) Re-infuse the expanded T-cell population into the patient (like a blood transfusion)
  - 6) The newly engineered T-cells further grow in the patient and, armed with their new machinery, attack the cancer entrenched in the body

NCI. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. 31 Aug 2017

CAR-T CONCEPTS

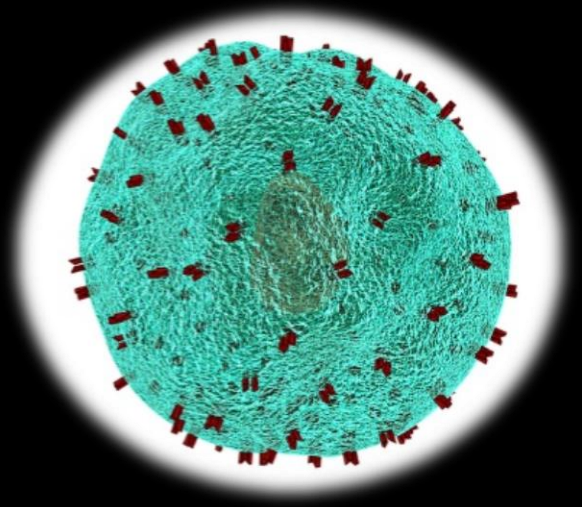


NCI. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. 31 Aug 2017

CAR-T CONCEPTS

- Success in Acute Lymphoblastic Leukemia
  - Common leukemia in children and young adults
  - High rates of cure with chemotherapy, stem cell transplants
  - Minimal success if these standard therapies fail

  - In the first trial in ALL with CAR-T cell therapy:
    - 27/30 (90%) patients went into complete remission initially
    - 18/30 (60%) were able to maintain this remission



- Early success in refractory lymphomas as well

Maude SL, et al. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. N Engl J Med 2014; 371:1507-1517.

CAR-T ADVERSE EVENTS

- Most feared side effect is cytokine release syndrome
  - Supraphysiologic response to immunotherapy
  - Manifestations:
    - Fever
    - Headache / Rash / Diarrhea / Myalgia / Arthralgia
    - Circulatory collapse
    - Altered mental status / Confusion

  - Management:
    - Based on the grade of CRS (hypotension, hypoxia)
    - Supportive care
    - Tocilizumab
    - Steroids

Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2016; 2016:567.

CONCLUSIONS

- Exciting times
- Options abound
- Novel approaches coupled with critical, science based rational drug & clinical trial design are poised to lead to further advances in our field
- Early recognition and appropriate management of these new classes of side effects are critical for patient success

THANKS!

(Nudge the person sitting next to you who looks like this)