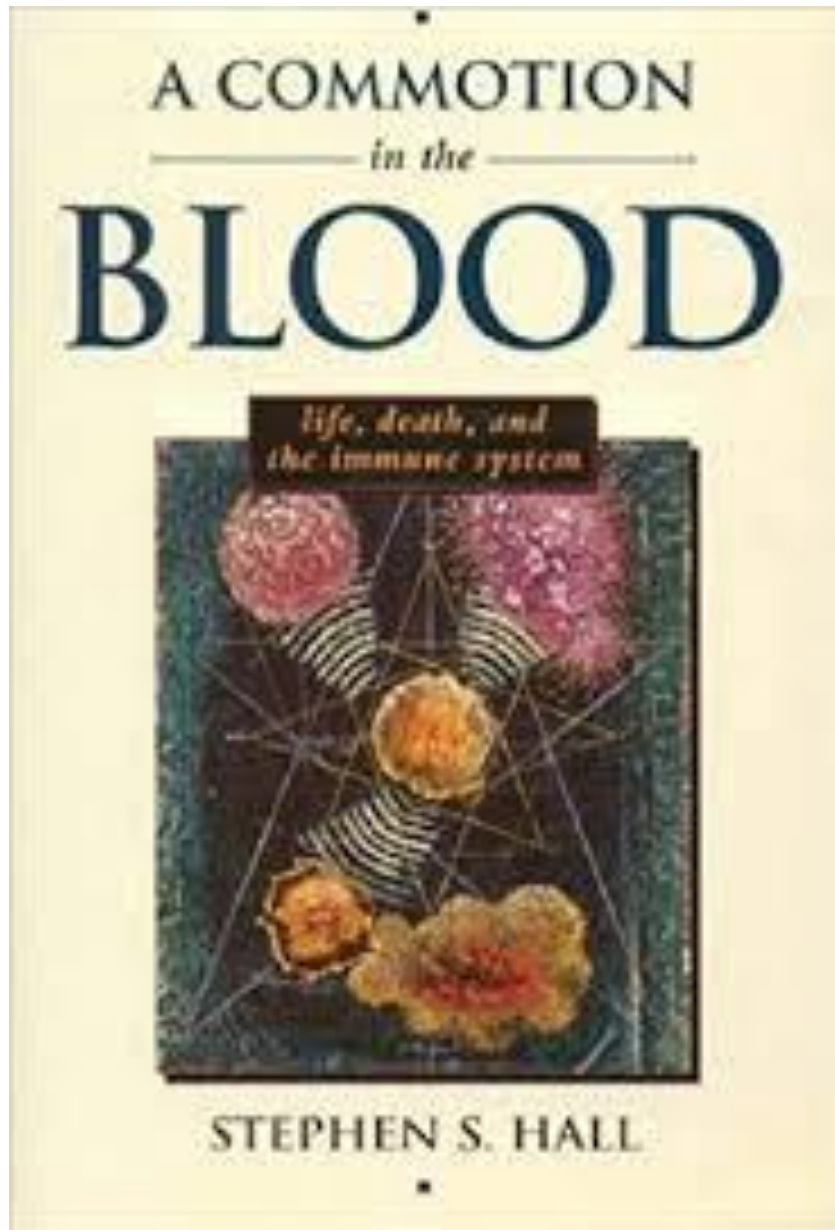




A Commotion in the Blood: Looking Back and Looking Forward to Immunotherapy of Cancer Coming of Age

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Director, Center for Damage Associated
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UPMC Hillman Cancer Center

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Cell: 412-478-3316

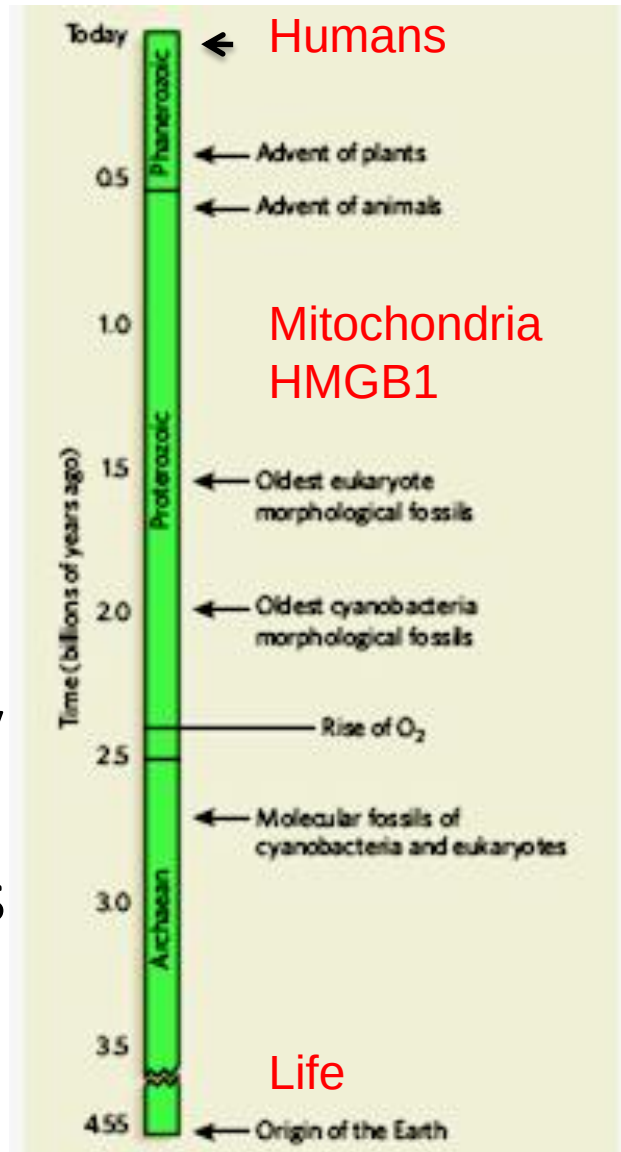
Disclosures-Consultant

- Prometheus
- **Celgene Cellular Therapeutics**
- NeuMedicine
- Chairman of the Advisory Board, Immunocellular Therapeutics, Ltd.
- Intezyne
- VeraStem
- Checkmate, Inc.
- Pieris, Inc.
- **Lion/Iovance CSO**
- **iRepertoire, Inc. (Hudson Alpha Institute)**
- Torque, Inc.
- Adicet, Inc.



History of Life

- $13.75 \pm 0.11\text{b}$ Universe
- 4.5b Planet Earth
- 4.0b Life on Earth
- 2.5b Toxic Gas Brought into Atmosphere by Cyanobacteria
- Molecular Oxygen!
- 1.0b Mitochondria Find Their Way into Our Ancestral Cells
- HMGB1 and Metacaspases Comes With Them or Shortly Behind – Where, When, & Why



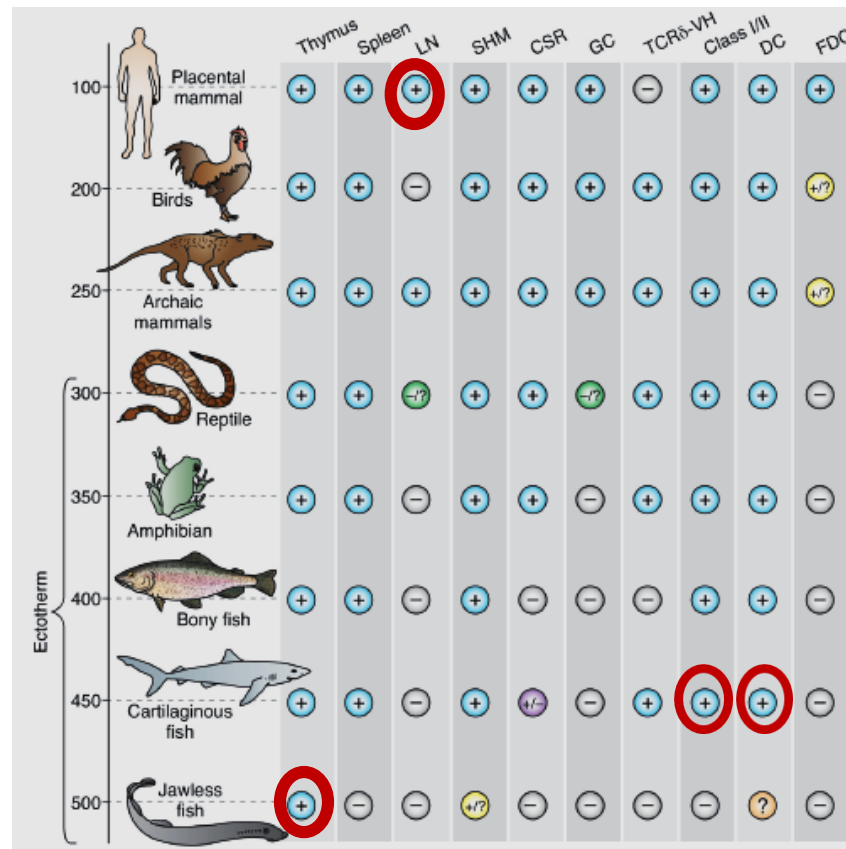
A cold-blooded view of adaptive immunity

Nature Review Immunology (2018)

Martin F. Flajnik Department of Microbiology and Immunology
University of Maryland Baltimore

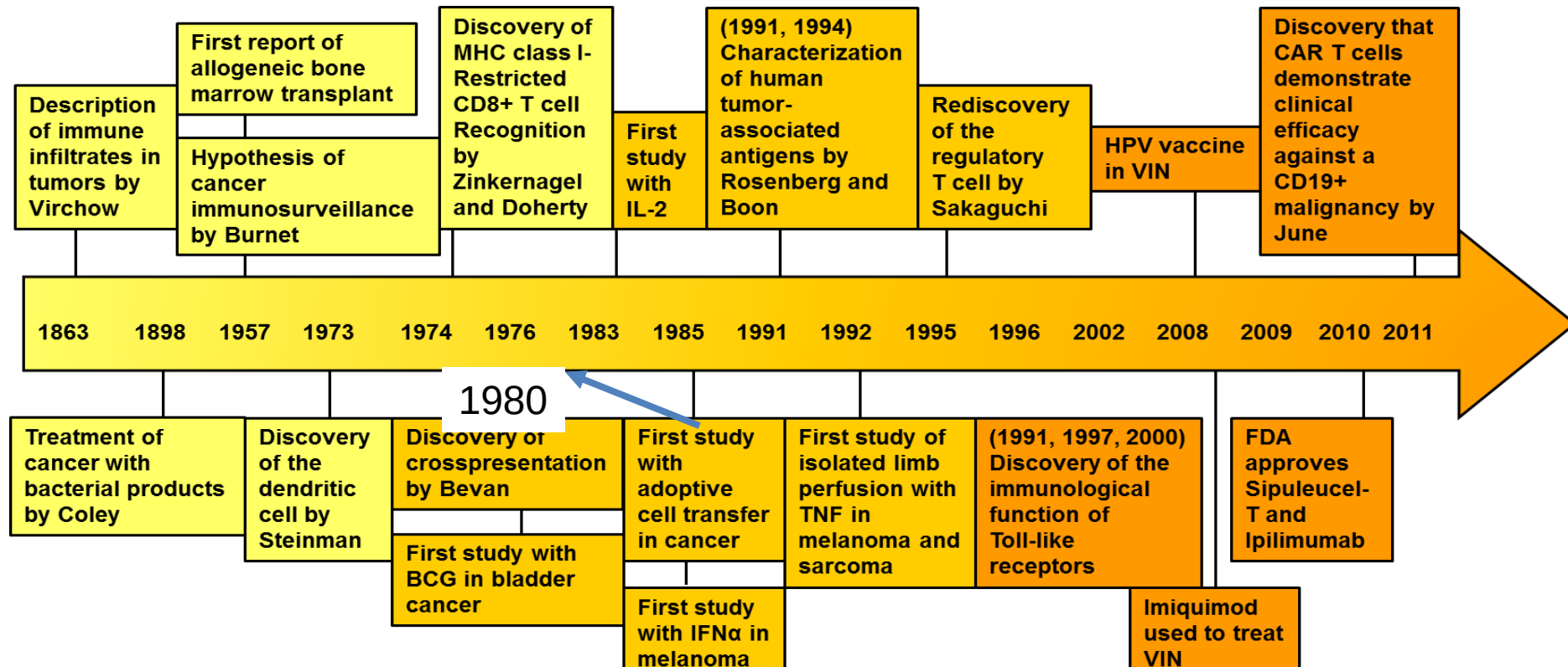
Innate immunity in single cell organisms (4byrs) evolved:

- 0) TLRs, NLRs, ALRs, RLRs, STING
- 1) engulf organisms by xenophagy;
- 2) develop 'adaptive' immunity involving CRISPR/Cas9;
- 3) toxic metabolites (yeast: alcohol; plants: salicylic acid and jasmonic acid) that limit pathogens; and
- 4) SIRP α /CD47.



NK cells and MHC-like molecules
(Maternal/Fetal interface): *Botryllus schlosseri* is a colonial invertebrate chordate (Urochordata) PNAS 2003 100:622-7.

History of Immunotherapy



1980

Anti-CD19 CAR T Cells Administered after Low-Dose Chemotherapy Can Induce Remissions of Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma
 James N Kochenderfer, Robert Somerville, Lily Lu, Alex Iwamoto, James C Yang, Christopher Klebanoff, Udai Kammula, Richard M Sherry, Shi Victoria, Constance Yuan, Steven Feldman, Tatyana Feldman, Andre Goy, Kathleen E Morton, Mary Ann Toomey and Steven A. Rosenberg
 Blood 2014 124:550;

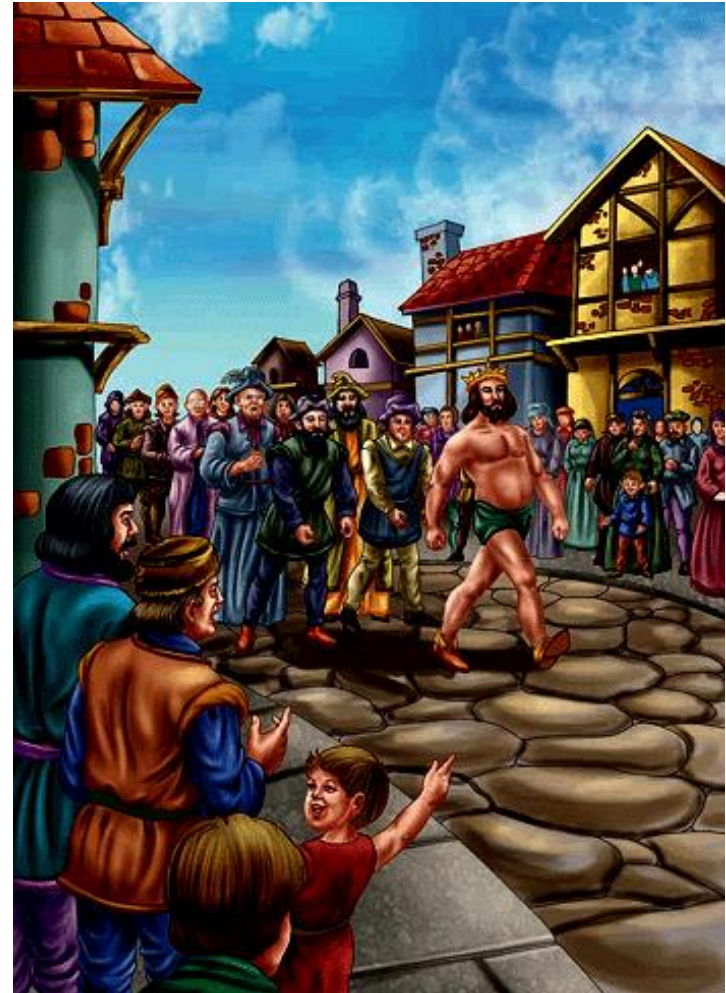
THE
EMPEROR
OF ALL
MALADIES



A BIOGRAPHY OF CANCER

SIDDHARTHA
MUKHERJEE

Emperors



The lymphocyte as a factor in natural and induced resistance to transplanted cancer.

Proc Natl Acad Sci U S A 1:435–437; 1915

Hence, it would seem fair to conclude that the lymphocyte is a necessary factor in cancer immunity – James B. Murphy and John J. Morton (Murphy and Morton 1915)

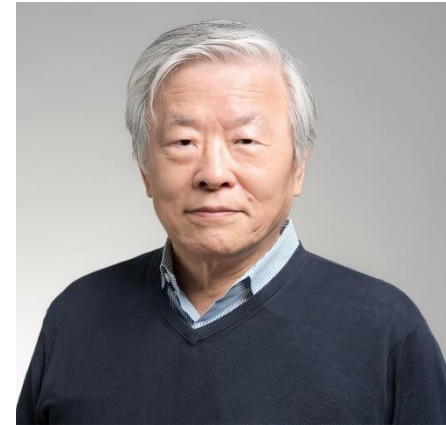


Rearranged Receptors in B and T Cells

Tonegawa S, et al. Evidence for somatic generation of antibody diversity. *Proc Natl Acad Sci U S A* 1974;71:4027-31.

Sakano H, Huppi K, Heinrich G, Tonegawa S. Sequences at the somatic recombination sites of immunoglobulin light-chain genes. *Nature* 1979;280:288-94.

Tonegawa S. Somatic generation of antibody diversity. *Nature* 1983;302:575-81.



Davis MM, Chien YH, Gascoigne NR, Hedrick SM. A murine T cell receptor gene complex: isolation, structure and rearrangement. *Immunol Rev* 1984;81:235-58.

Kavaler J, Davis MM, Chien Y. Localization of a T-cell receptor diversity-region element. *Nature* 1984;310:421-3.

Robertson M. Receptor gene rearrangement and ontogeny of T lymphocytes. *Nature* 1984;311:305-6.

Royer HD, Acuto O, Fabbi M, et al. Genes encoding the Ti beta subunit of the antigen/MHC receptor undergo rearrangement during intrathymic ontogeny prior to surface T3-Ti expression. *Cell* 1984;39:261-6.

Siu G, Kronenberg M, Strauss E, Haars R, Mak TW, Hood L. The structure, rearrangement and expression of D beta gene segments of the murine T-cell antigen receptor. *Nature* 1984;311:344-50.



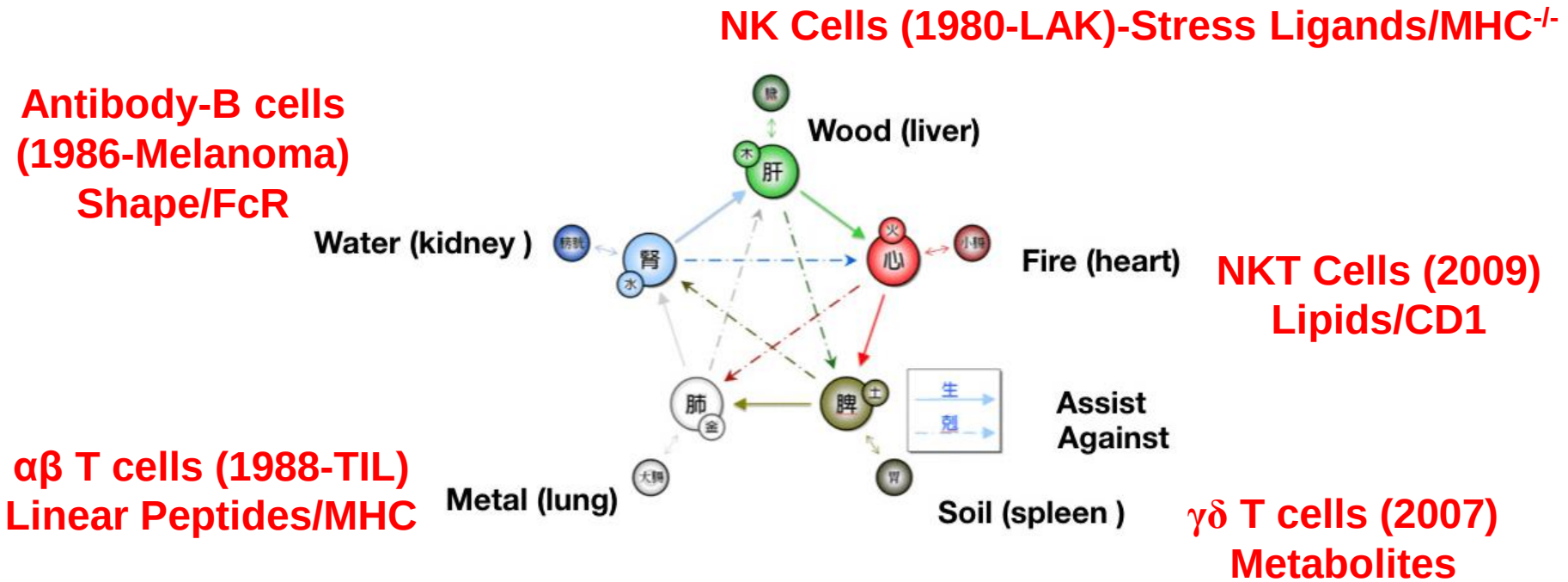
Hayday AC, Saito H, Gillies SD, et al. Structure, organization, and somatic rearrangement of T cell gamma genes. *Cell* 1985;40:259-69.

Lefranc MP, Rabbitts TH. Two tandemly organized human genes encoding the T-cell gamma constant-region sequences show multiple rearrangement in different T-cell types. *Nature* 1985;316:464-6.



500 Million Years of Adaptive Immunity-Wu Xing

The Immunologic Big Bang



The Immunologic Big Bang

Pillars of Immunology

The Journal
of Immunology

A Convergent Immunological Holy Trinity of Adaptive Immunity in Lampreys: Discovery of the Variable Lymphocyte Receptors

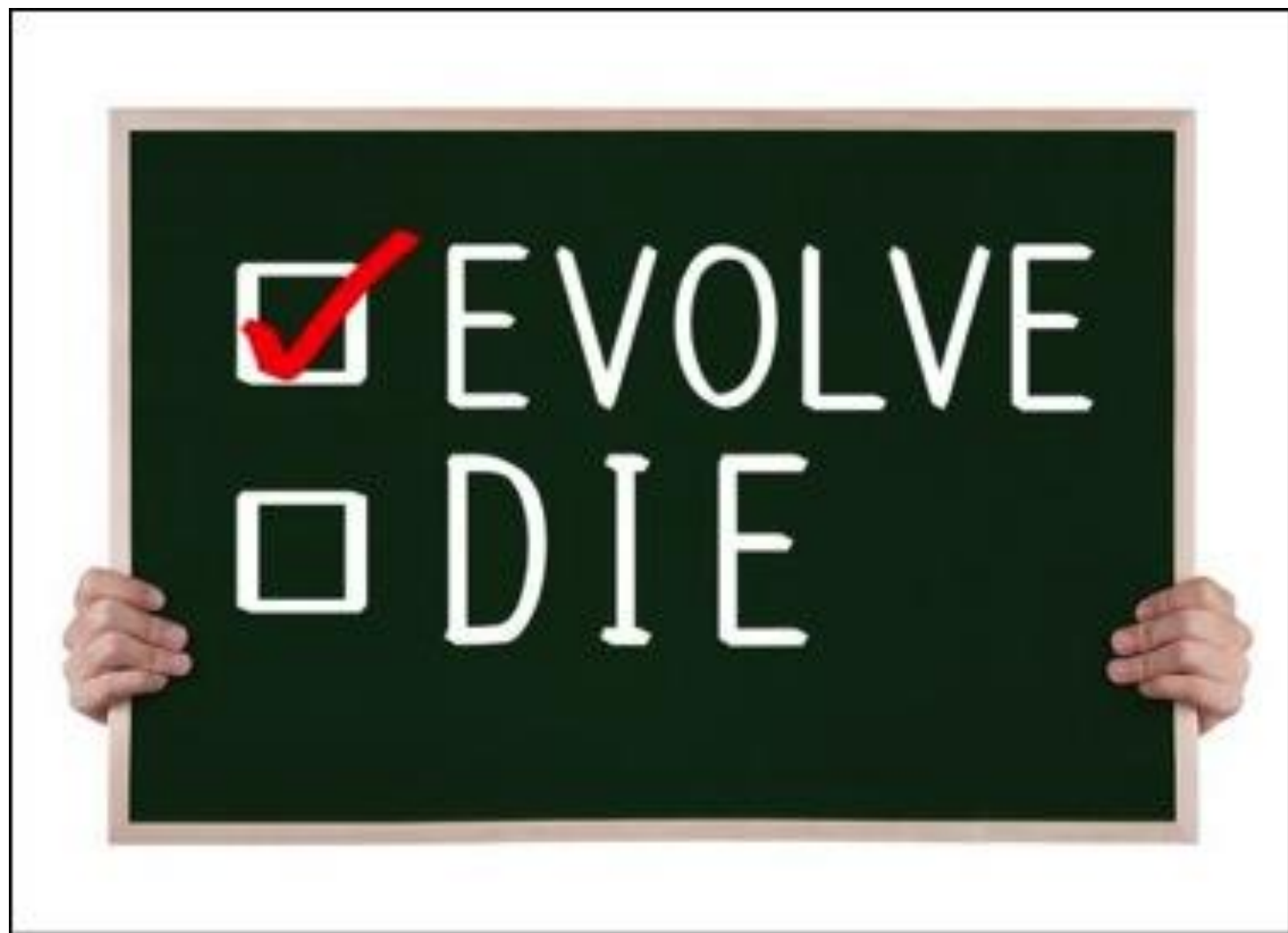
Martin F. Flajnik

doi: 10.4049/jimmunol.1800965
J Immunol 2018; 201:1331-1335



Zeev Pancer and Max Cooper With a Larval Lamprey at UAB.



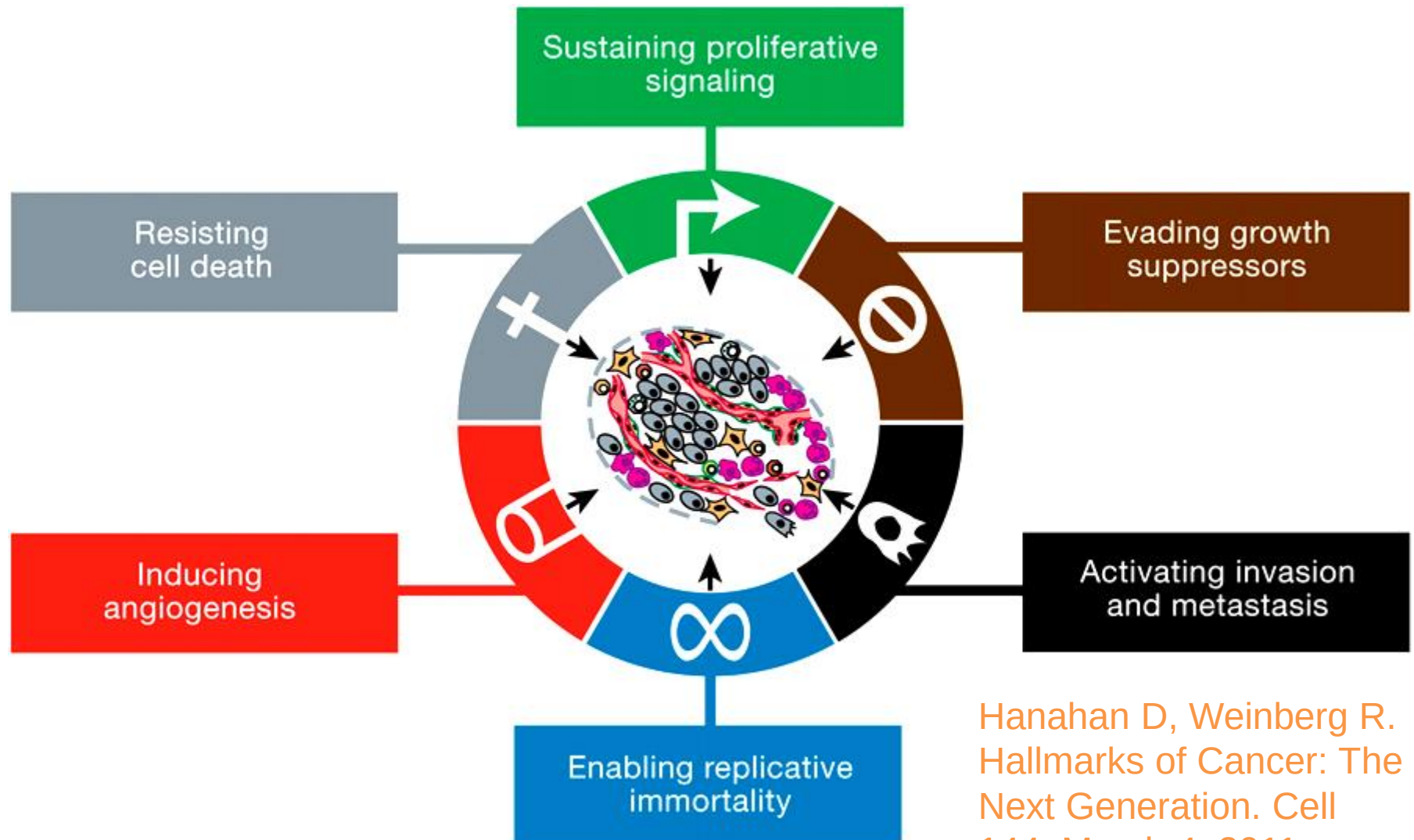


The Hellström Paradox

- A paradox lies at the heart of cancer.
- Coursing through many tumors are legions of immune cells, including the T cells that should be fighting the cancer.
- Yet these T cells are typically dysfunctional — they stop working and let the tumor grow with abandon.
- Scientists have a name for this conundrum: the Hellström paradox, after Ingegerd and Karl

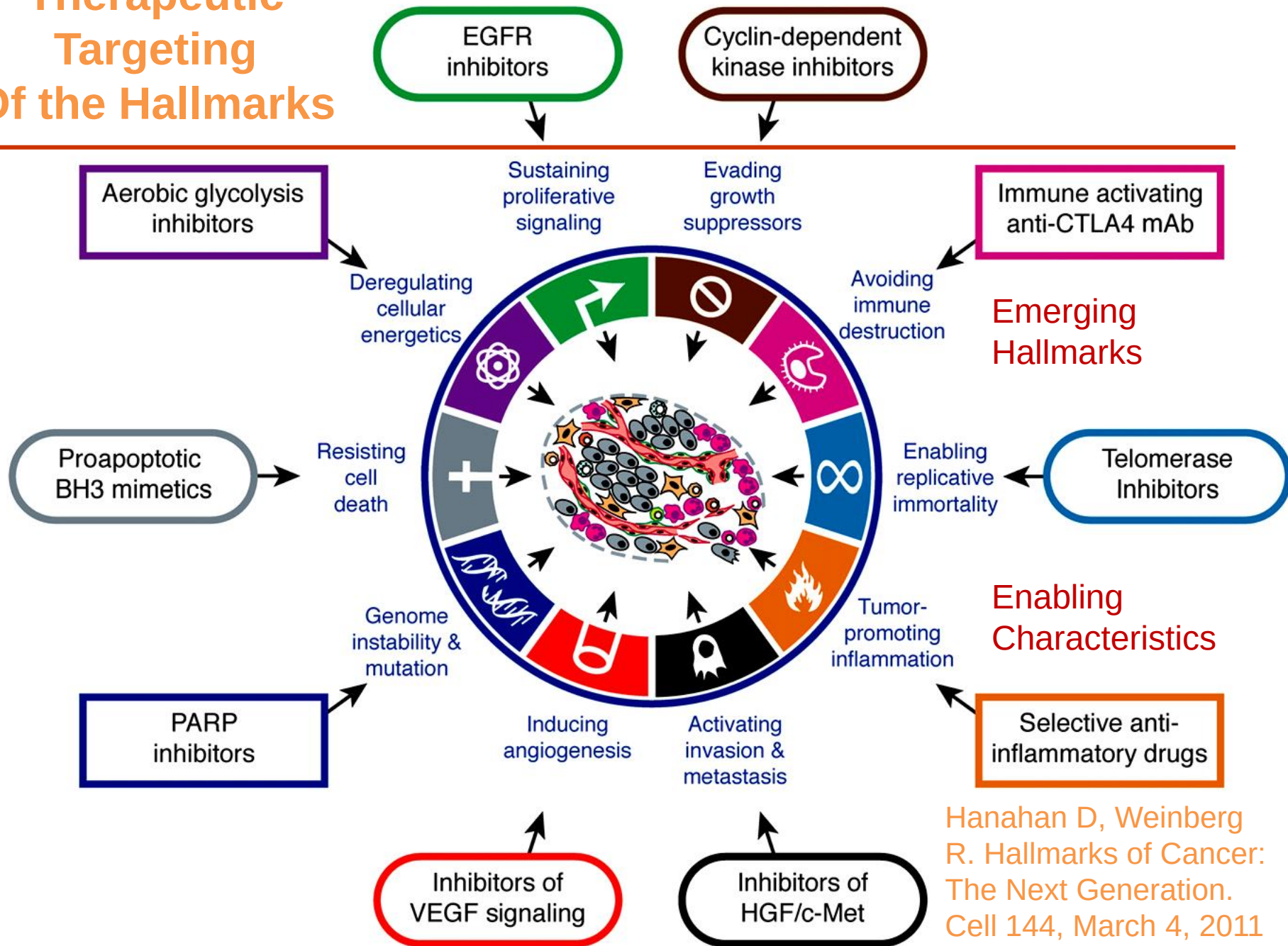


Original Hallmarks of Cancer



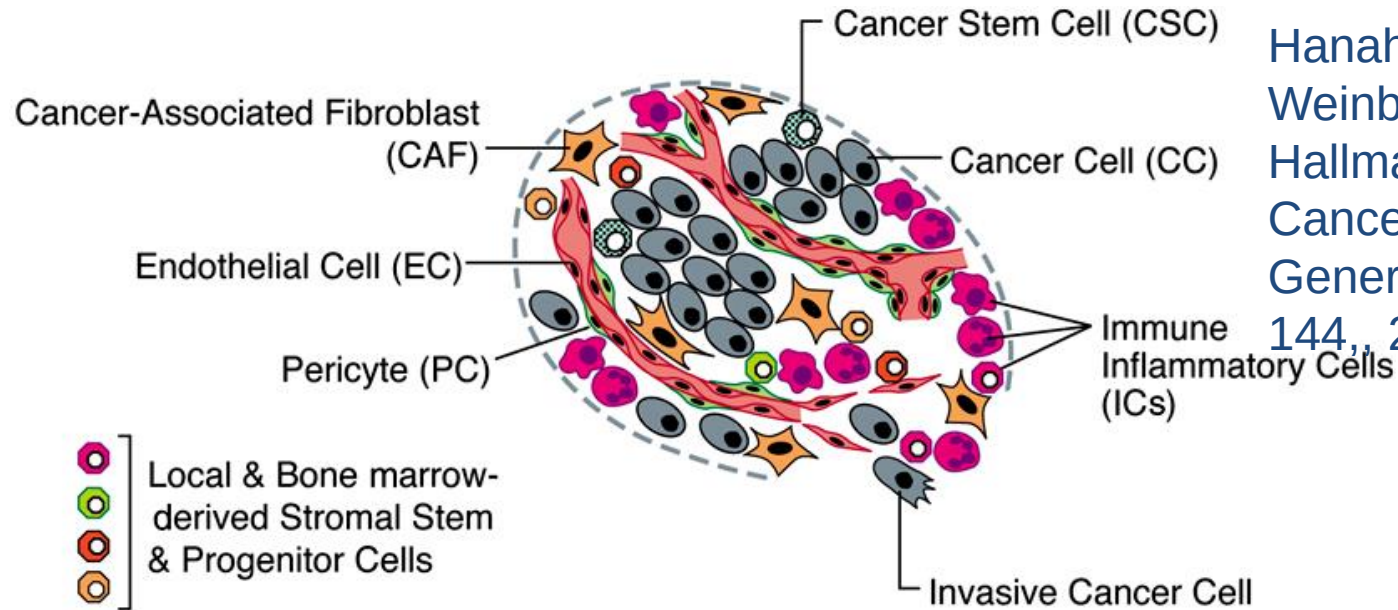
Hanahan D, Weinberg R.
Hallmarks of Cancer: The
Next Generation. Cell
144, March 4, 2011

Therapeutic Targeting Of the Hallmarks

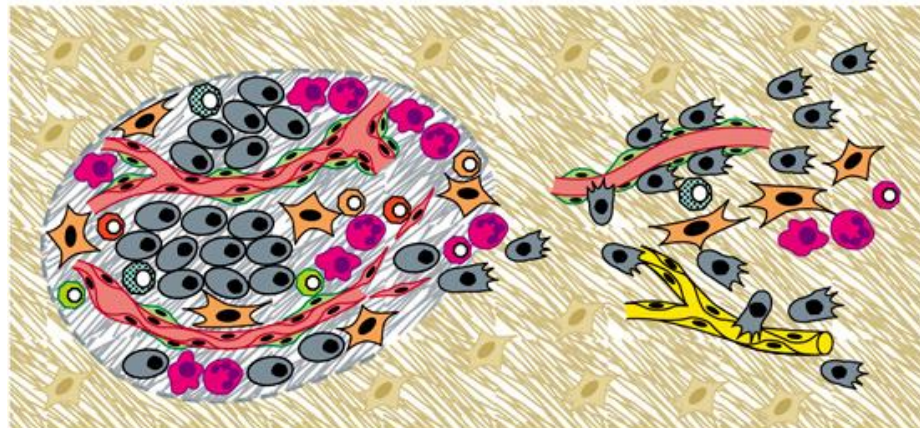


Hanahan D, Weinberg R. Hallmarks of Cancer: The Next Generation. Cell 144, March 4, 2011

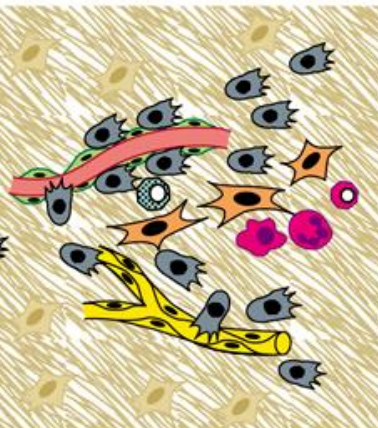
The Cells of the Tumor Microenvironment



Hanahan D,
Weinberg R.
Hallmarks of
Cancer: The Next
Generation. Cell
144, 2011



Core of Primary Tumor
microenvironment



Invasive Tumor
microenvironment



Metastatic Tumor
microenvironment



Look!
Stem cells!

Art by Mike Fishers

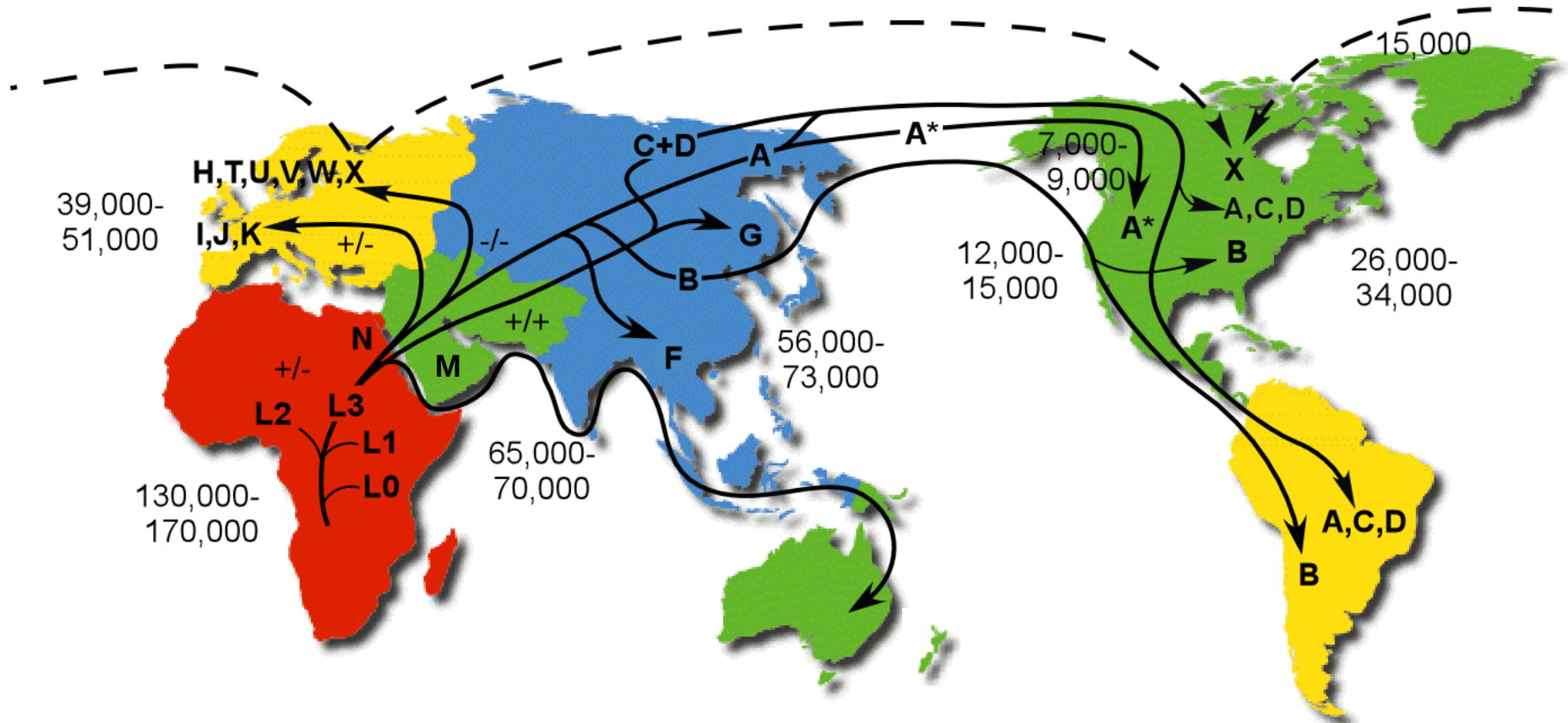
BIZARROCOMICS.COM Facebook.com/BizarroComics

P. TIRAPÓ
1.11.13

HUMAN MIGRATIONS: NON-RANDOM DISTRIBUTION OF mtDNA VARIATION SUGGESTS SELECTION

Striking Discontinuities:

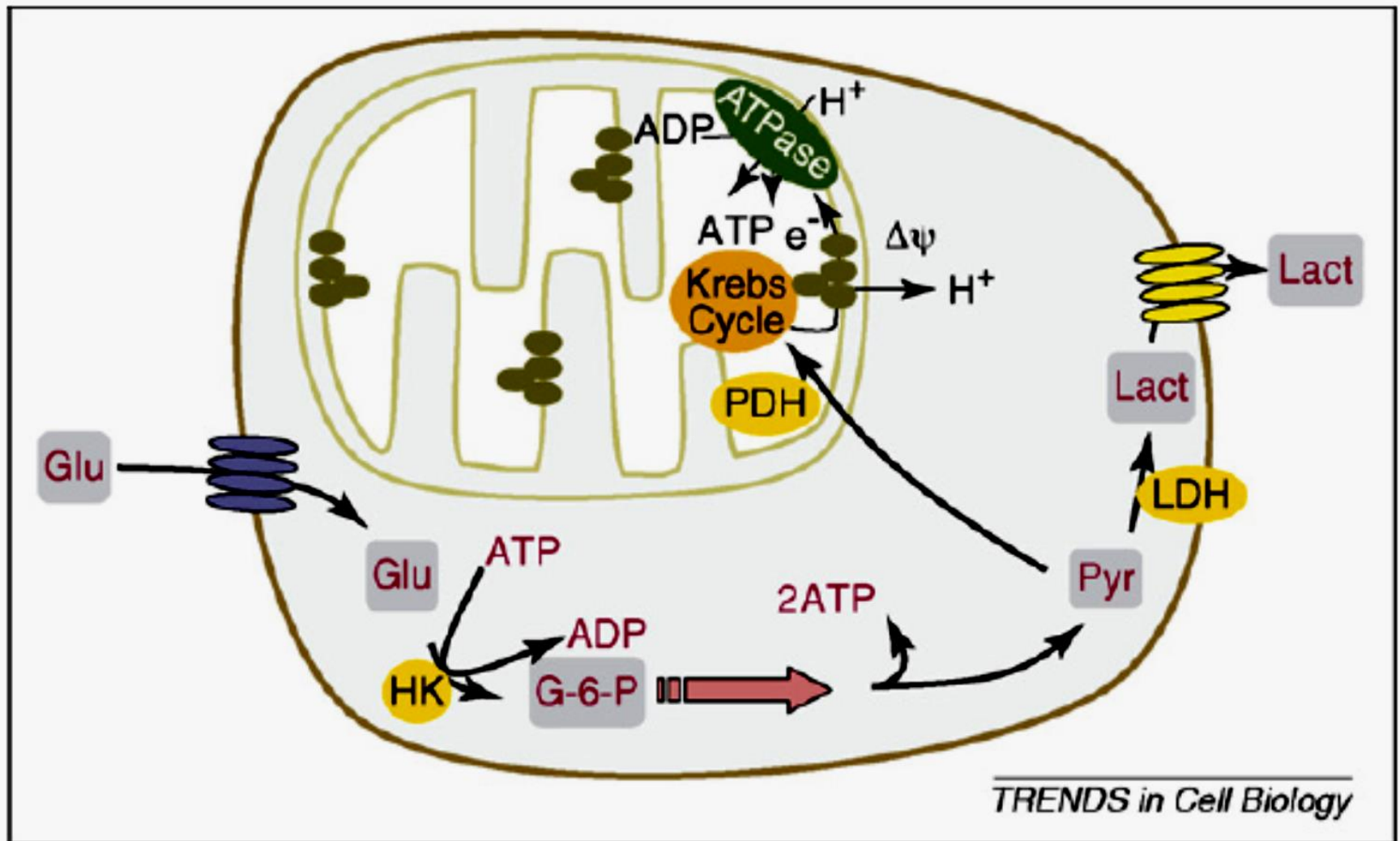
Tropical Africa to Temperate Eurasia to Arctic Siberia



+/-, +/+, or -/- = Dde I 10394 / Alu I 10397
* = Rsa I 16239

Mutation rate = 2.2 – 2.9% / MYR
Time estimates are YBP.

“Hybrid Metabolism” - Glycolysis And OXPHOS



24 February 1956, Volume 123, Number 3191

SCIENCE

On the Origin of Cancer Cells

Otto Warburg

1 Glucose → 36 ATP [Slow]

Or

1 Glucose → 2 ATP + 2 NADH + 2 Pyruvate [Fast]

Injuring of Respiration





Otto Warburg

The Nobel Prize in Physiology or Medicine
1931

For his discovery of cellular combustion, which he termed cellular respiration.

Warburg hypothesis: tumor cells have **dysfunctional mitochondria** and show an **increase in glycolysis** that is maintained in conditions of high **oxygen tension** (“**aerobic glycolysis**”), giving rise to enhanced lactate production.

Over the last 70 years his ideas have come, gone and now have been revitalized...



Dr. Otto Warburg

Antrag

Ich benötige 10 000 (zehntausend) Mark

Otto Warburg

Grant proposal: "I require 10,000 marks"



The Beginning of Molecular Therapeutics - 1978

PEOPLE.COM • ARCHIVE

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

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

History of SITC

- 1980-1984 NCI Frederick Biologic Response Modifiers (nonspecific immunotherapies) - Journal of Biologic Response Modifiers (1982); Society for Biologic Therapy (1984)
- 1985 Cytokine Therapeutics – 1st Annual Meeting of SBT (1986)
- 1990's Antibody (Her2, CD20, VEGF, etc.) Therapeutics – First Primer on Tumor Immunology (1998, Pittsburgh); Executive Director Inc (Tara Withington)
- 2000's Cancer Vaccines - iSBTc (2002); SITC (2010)
- 2010's Cell Therapies (TIL, CART, DC, NK/NKT, etc.) - Journal for ImmunoTherapy of Cancer (2013)
- 2015 Checkpoint Inhibitors; Oncolytic Viruses/Cytokines
- 2019+ The Future Just Ain't What it Used to be (Yogi Berra) - Cancer Immunotherapy Winter School (2019); 34th Annual Meeting (2019)





Cancer Immunotherapy



2013



2014



James Allison
Immunotherapy
Nobel Prize 2018



Yoshinori Ohsumi
Autophagy
Nobel Prize 2016



Tasuku Honjo
Immunotherapy
Nobel Prize 2018

Japanese scientist Yoshinori Ohsumi was awarded this year's Nobel Prize in medicine on Monday for discoveries related to the degrading and recycling of cellular components. The Karolinska Institute honored Ohsumi for "brilliant experiments" in the 1990s on autophagy, the machinery with which cells recycle their content. Disrupted autophagy has been linked to various diseases, including Parkinson's, diabetes and cancer, the institute said. Ohsumi was born in 1945 in Fukuoka, Japan. He is currently a professor at the Tokyo Institute of Technology.

Disturbance of function (*functio laesa*): the legendary 5th cardinal sign of inflammation, added by Galen to the four cardinal signs of Celsus.

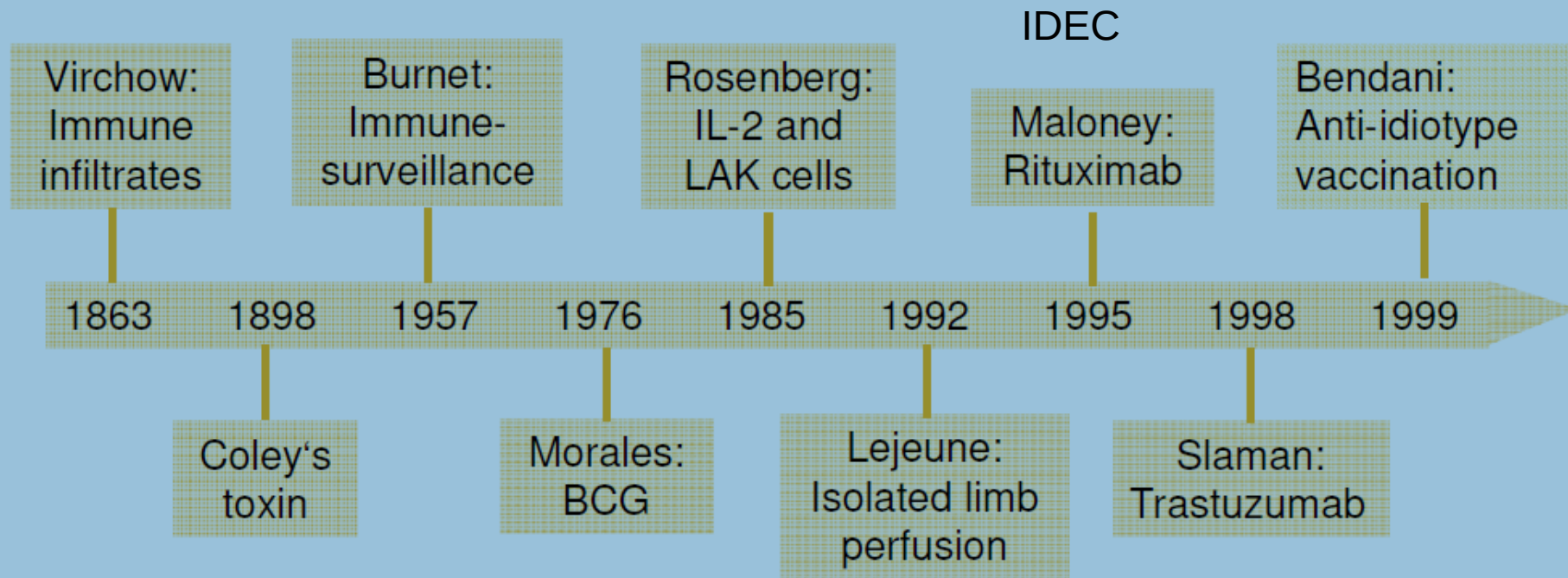
Rather LJ. Bull N Y Acad Med. 1971.



Calor (warmth), *dolor* (pain), *tumor* (swelling) and *rubor* (redness), and (later) loss of function
Celsus, *De Medicina*



Before There were Checkpoints



Coley's Toxins, 1893



Fig. 2. Patient as he first appeared to Coley in 1891, 7 years after the accidental erysipelas-induced regression of inoperable sarcoma (Coley, 1893a).

W. Busch.
Einfluß von
Erysipel.
Berliner
Klin Wschr
1866. 3:
245–246.

Complete remission of a sarcoma in
a patient after 2 episodes of
erysipelas caused by
streptococcus pyogenes

William Coley, 1893

First 40 Yrs of Cancer Immunotherapy

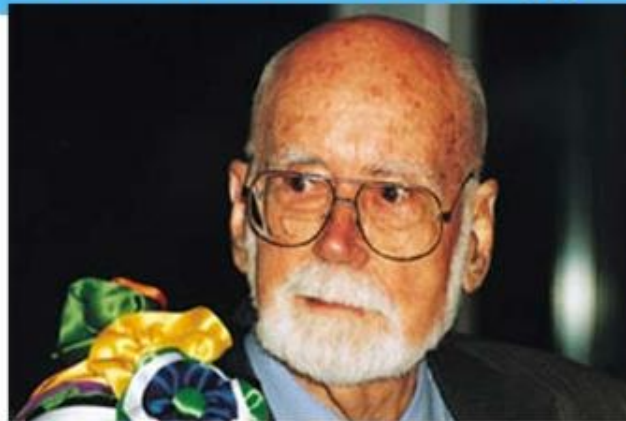


Steven
Rosent

IL-2 Activ
NK/LAK (C
Infuse

197

E. Donnall Thomas
The Nobel Prize, 1990



first successful HSCT in treatment of acute leukemias

Cooperstown, NY Mary Imogene Bassett Hospital T-cells

Thomas ED, Lochte HL, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy.

N. Engl. J. Med. 1957; 257: 491

64

7/14/2014

Pubmed: >333,889 articles about tumor immunology

1984 Beta, 'alpha'=gamma, alpha,
delta (1987)



as
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8

kpoints

2014
PD-1

Cytokine Working Group

CWG: The Abbreviated History (SITC 2018)

David McDermott, MD

Beth Israel Deaconess Medical Center

Dana Farber/Harvard Cancer Center

Harvard Medical School



Beth Israel Deaconess
Medical Center



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL



A founding member of
**Dana-Farber/Harvard
Cancer Center**

Adaptive Immune System

Humoral (B cells):

IgH (M, D, G, A, E) and $\kappa\lambda$ light chains; Antibodies recognize three-dimensional regions (epitopes) on intact protein, carbohydrate, nucleotide, or lipid molecules.

Cellular (T cells, NK Cells, NKT cells):

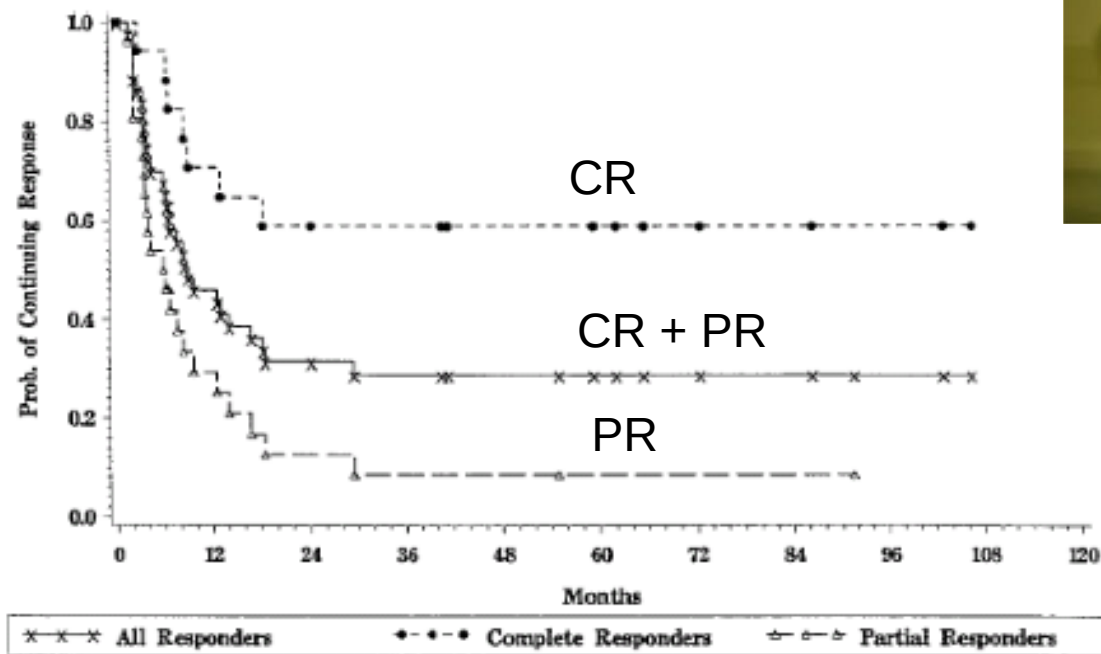
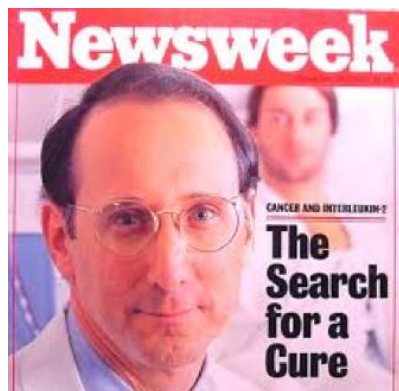
$\alpha\beta$ Recognize peptides that result from the degradation of intracellular proteins and are presented on cell surface MHC molecules.

$\gamma\delta$ Recognize phosphoantigens, metabolites from pathogens and stressed host cells

NKT Recognize lipid in CD1 (MHC homologues)

NK Recognize stress, lack of MHC molecules

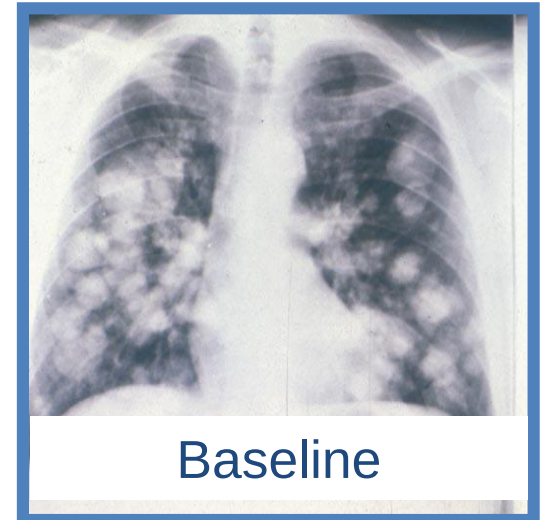
Proof of Principle: Deep responses produce remissions



Atkins, Lotze et al. J Clin Oncol. 1999

High Dose IL-2 Immunotherapy

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



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

Interleukin-2 in a

Jeffery R. Weiss,
David Ernstoff,
Michael Mier,

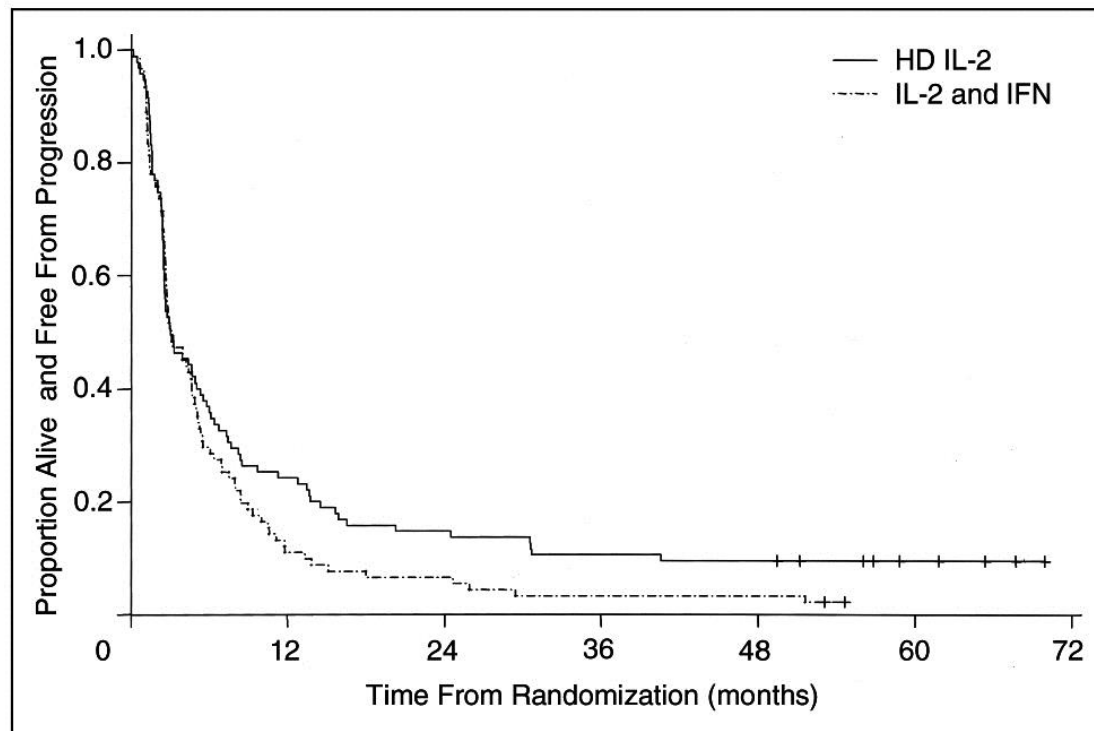


Fig 2. Progression-free survival by treatment arm among 186 patients receiving high-dose interleukin-2 (HD IL-2; $n = 95$) or receiving IL-2 and interferon alfa-2b (IFN; $n = 91$). Ten patients receiving HD IL-2 remained progression-free at 3 years compared with three patients who received IL-2 and IFN ($P = .082$ by Fisher's exact test).

The High-Dose Aldesleukin "Select" Trial: A Trial to Prospectively Validate Predictive Models of Response to Treatment in Patients with Metastatic Renal Cell Carcinoma

Table 3. Response by baseline clinical/tumor characteristics

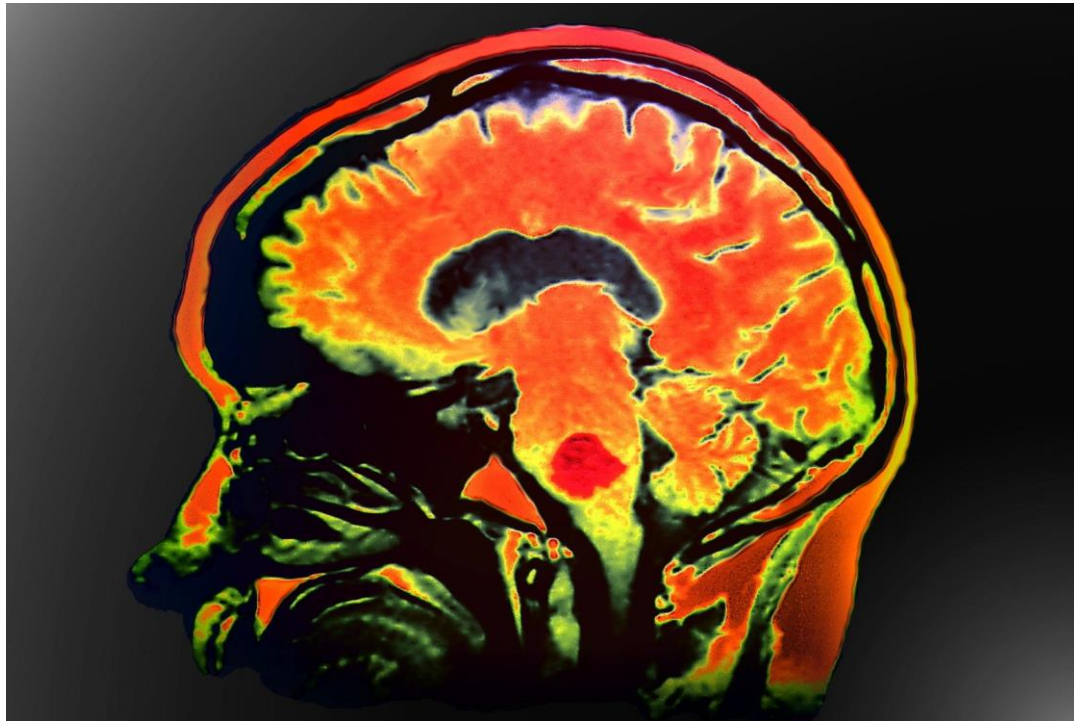
	ORR (95% CI)	<i>P</i> ^a	PFS > 3 y (95% CI)	<i>P</i> ^a
Clinical characteristics				
MSKCC risk group				
Favorable (<i>n</i> = 23)	22% (7%–44%)	0.89	17% (5%–39%)	0.33
Intermediate (<i>n</i> = 84)	25% (16%–36%)		8% (3%–17%)	
Poor (<i>n</i> = 13)	31% (9%–61%)		15% (2%–45%)	
UCLA SANI Score				
Low (<i>n</i> = 10)	20% (3%–56%)	0.27	10% (0%–45%)	0.84
Intermediate (<i>n</i> = 102)	27% (19%–37%)		12% (6%–20%)	
High (<i>n</i> = 8)	0% (0%–37%)		0% (0%–37%)	
Tumor characteristics				
Tumor type				
Clear cell (<i>n</i> = 114)	26% (19%–35%)	0.33	12% (6%–19%)	0.99
Non-clear cell (<i>n</i> = 5)	0% (0%–52%)		0% (0%–52%)	
Clear cell histology risk group				
Good (<i>n</i> = 11)	27% (6%–61%)	0.89	18% (2%–52%)	0.58
Intermediate (<i>n</i> = 83)	24% (15%–35%)		10% (4%–18%)	
Poor (<i>n</i> = 25)	28% (12%–49%)		12% (3%–31%)	
CA-9 score				
High (≥85% <i>n</i> = 78)	22% (13%–33%)	0.19	9% (4%–18%)	0.35
Low (<85% <i>n</i> = 39)	33% (19%–50%)		15% (6%–31%)	
ISM risk group				
Good (<i>n</i> = 74)	23% (14%–34%)	0.39	9% (4%–19%)	0.55
Poor (<i>n</i> = 43)	30% (17%–46%)		14% (5%–28%)	
PD-L1 ⁺ tumor				
Negative (<i>n</i> = 95)	19% (12%–28%)	0.01	6% (2%–13%)	<0.01
Positive (<i>n</i> = 18)	50% (26%–74%)		33% (13%–59%)	
B7-H3 ⁺ tumor				
Negative (<i>n</i> = 28)	11% (2%–28%)	0.08	7% (1%–24%)	0.73
Positive (<i>n</i> = 86)	29% (20%–40%)		12% (6%–20%)	
CA-9 SNP				
Homozygous (<i>n</i> = 66)	20% (11%–31%)	0.28	12% (5%–22%)	0.35
Variant (<i>n</i> = 12)	33% (10%–65%)		0% (0%–26%)	

NOTE: The numbers (*n*) for each analysis do not always add up to 120 patients as data/tissue were not available in some cases.

^aFisher exact test.

Immunotherapy Drugs Slow Skin Cancer That Has Spread to the Brain

NYT August 22, 2018



CANCER, DEALS

As drugmakers seek ways to elude IL-2 flaws, Clinigen secures the full rights to original troubled IL-2 drug Proleukin



by **NATALIE GROVER**  — on February 13, 2019 07:15 AM EST

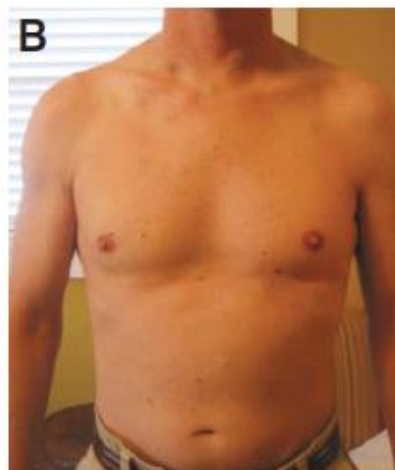
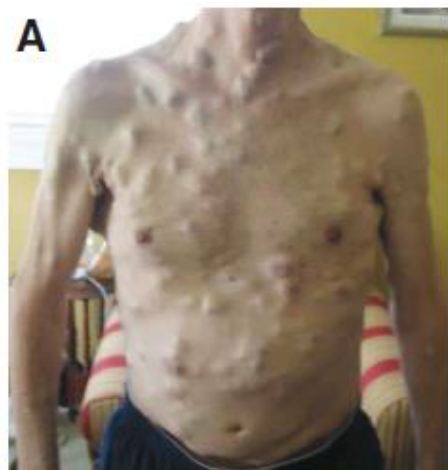
Updated: 11:58 AM



Proleukin, the troubled IL-2 cancer drug sold by Novartis, has found a new home at Clinigen, while [others](#) in the field of immuno-oncology seek ways to create an [improved version](#) of the class of drugs sans the toxicity that has stymied the use of the original IL-2.

The best pla
POINTS NE
Comprehensive

Vemurafenib Response in V600E Mutant Melanoma



And Photograph "C" was taken after relapse, after 23 weeks of therapy with vemurafenib.



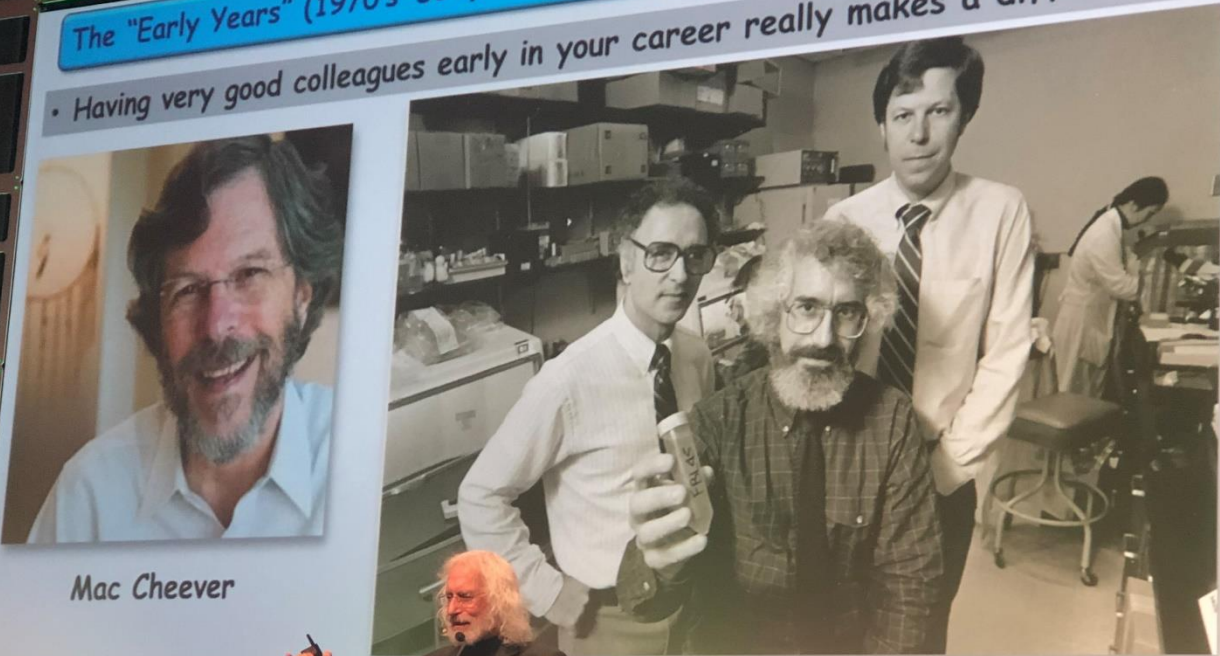
After 15 weeks what if this patient had been given a chance at long term response with Proleukin?



Cheever, Greenberg, Fefer

The "Early Years" (1970's-80's): Developing T cell therapy in mouse models

- Having very good colleagues early in your career really makes a difference

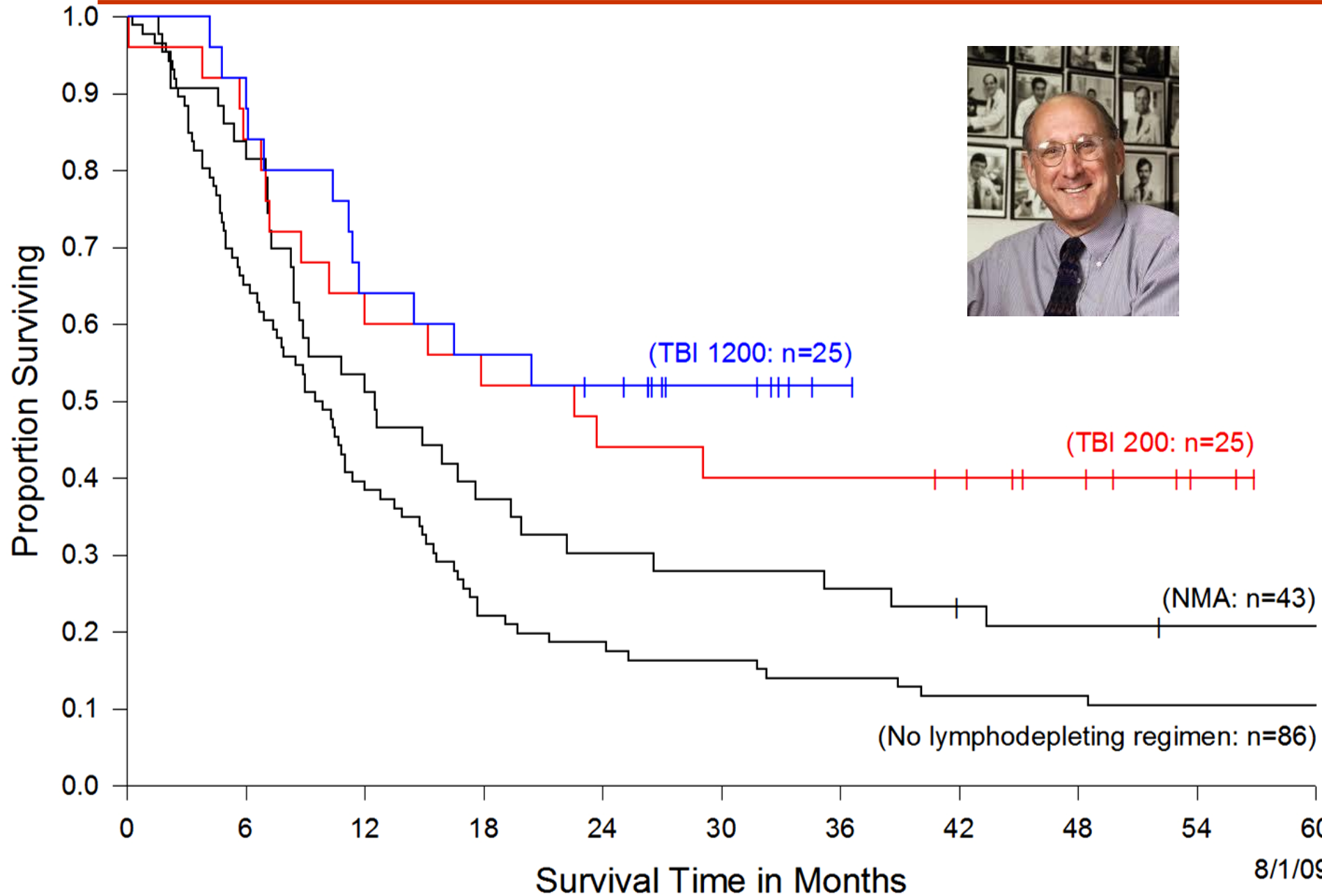


Mac Cheever

SITC 2018

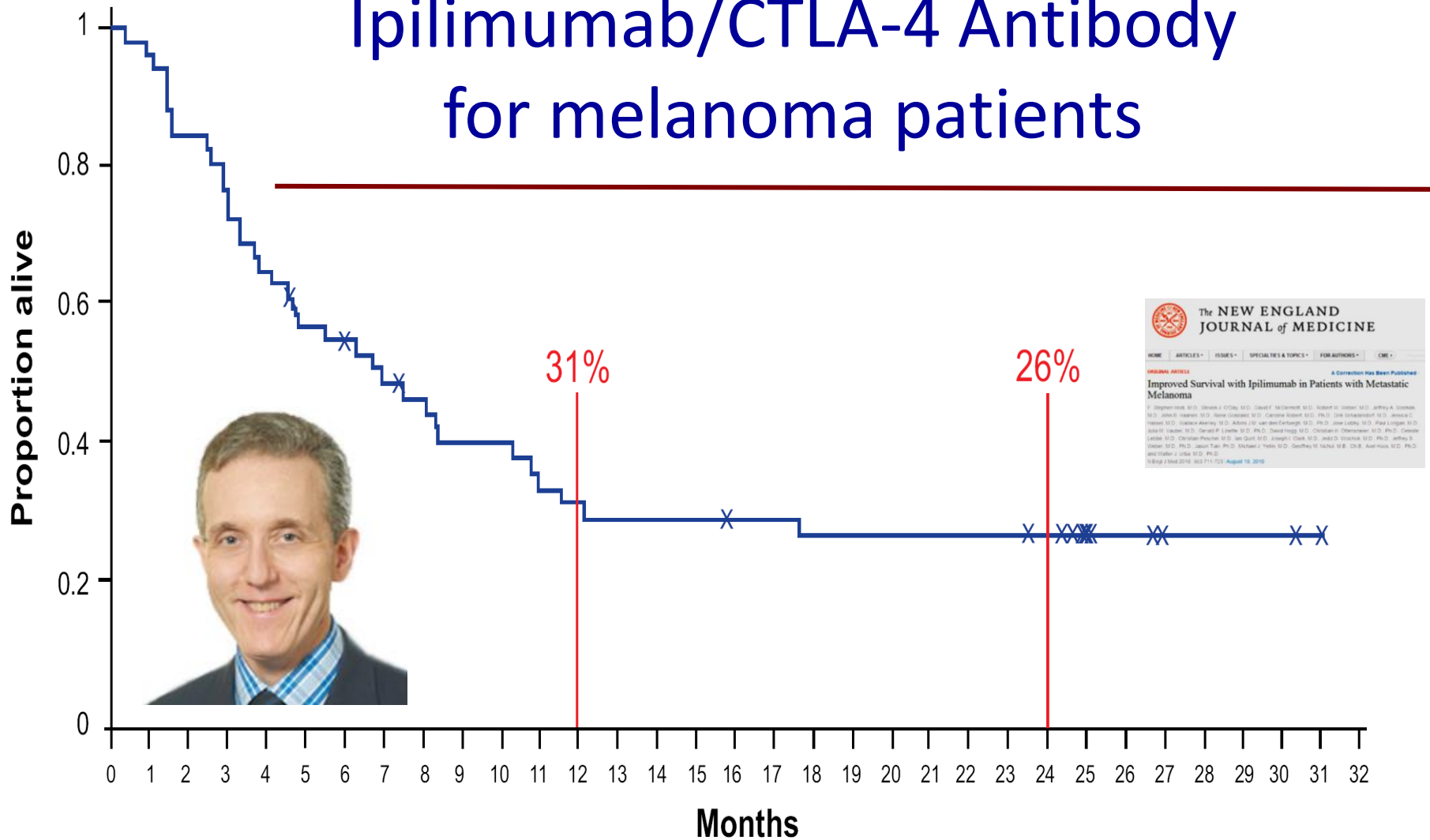
The image shows a presentation slide with a blue header and a grey bullet point. Below the text are two photographs. The left photo is a portrait of a man with a beard and glasses, identified as Mac Cheever. The right photo is a group of three men in a laboratory setting; the man in the center is holding a vial labeled 'T-RAE'. In the foreground, a man with white hair and glasses is speaking at a podium that has 'SITC 2018' on it. The background of the slide is decorated with a green and black geometric pattern.

Survival of Patients with Metastatic Melanoma Treated with Autologous Tumor Infiltrating Lymphocytes and IL-2





Ipilimumab/CTLA-4 Antibody for melanoma patients

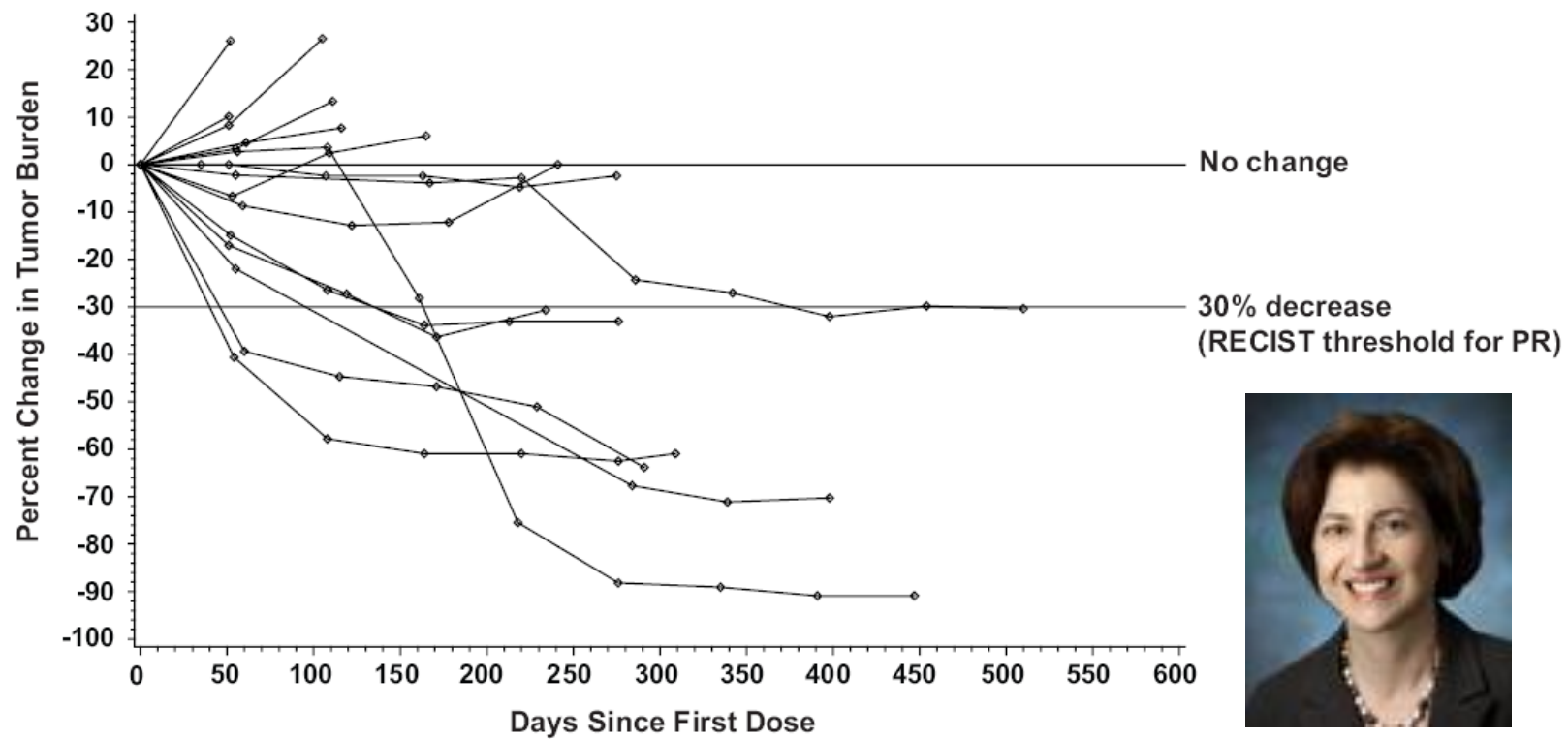


Patients at risk

51 49 43 38 33 28 27 23 21 18 18 15 14 13 13 13 12 12 11 11 11 11 11 11 11 10 7 4 2 2 2 2 1 0

x = censored data

PD1 AB RESULTS: RCC PATIENTS



*Patients treated at the 10 mg/kg dose



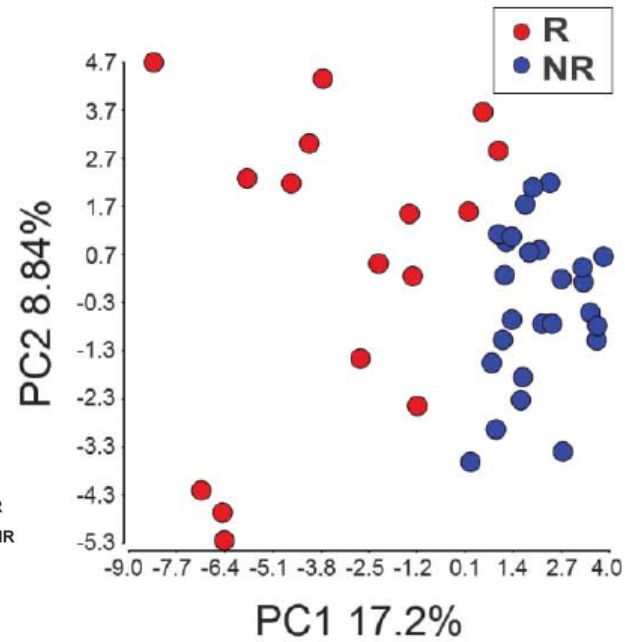
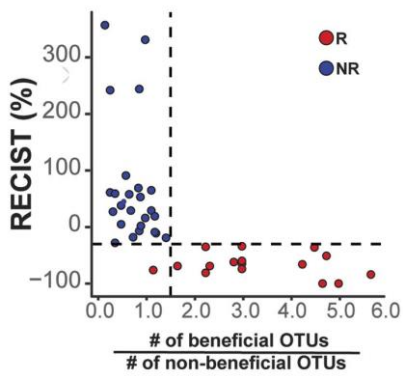
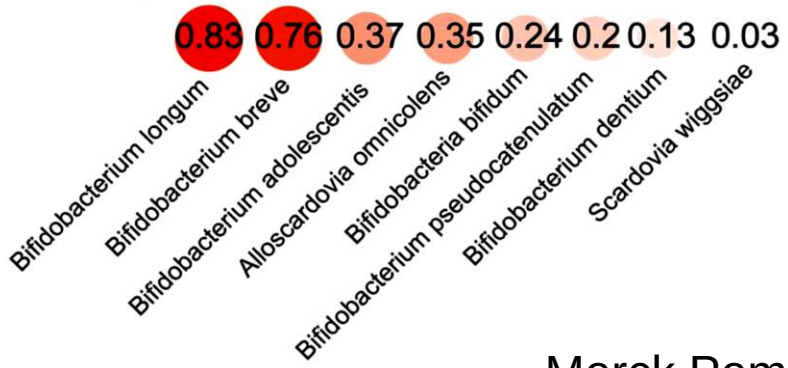


CANCER IMMUNOTHERAPY

The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients

Vyara Matson,^{1*} Jessica Fessler,^{1*} Riyue Bao,^{2,3*} Tara Chongsuwat,⁴ Yuanyuan Zha,⁴ Maria-Luisa Alegre,⁴ Jason J. Luke,⁴ Thomas F. Gajewski^{1,4†}

559527|Bifidobacteriaceae



Operational
Taxonomic
Units

Merck Pembro Anti-PD1 + *Bifidobacterium longum*



Why science teachers
should not be given
playground duty.

BACKUPS

What is Cancer Immunotherapy?

- **A type of cancer treatment designed to boost the body's natural defenses to fight the cancer.**
- **It uses substances either made by the body or in a laboratory to improve or restore immune system function.**

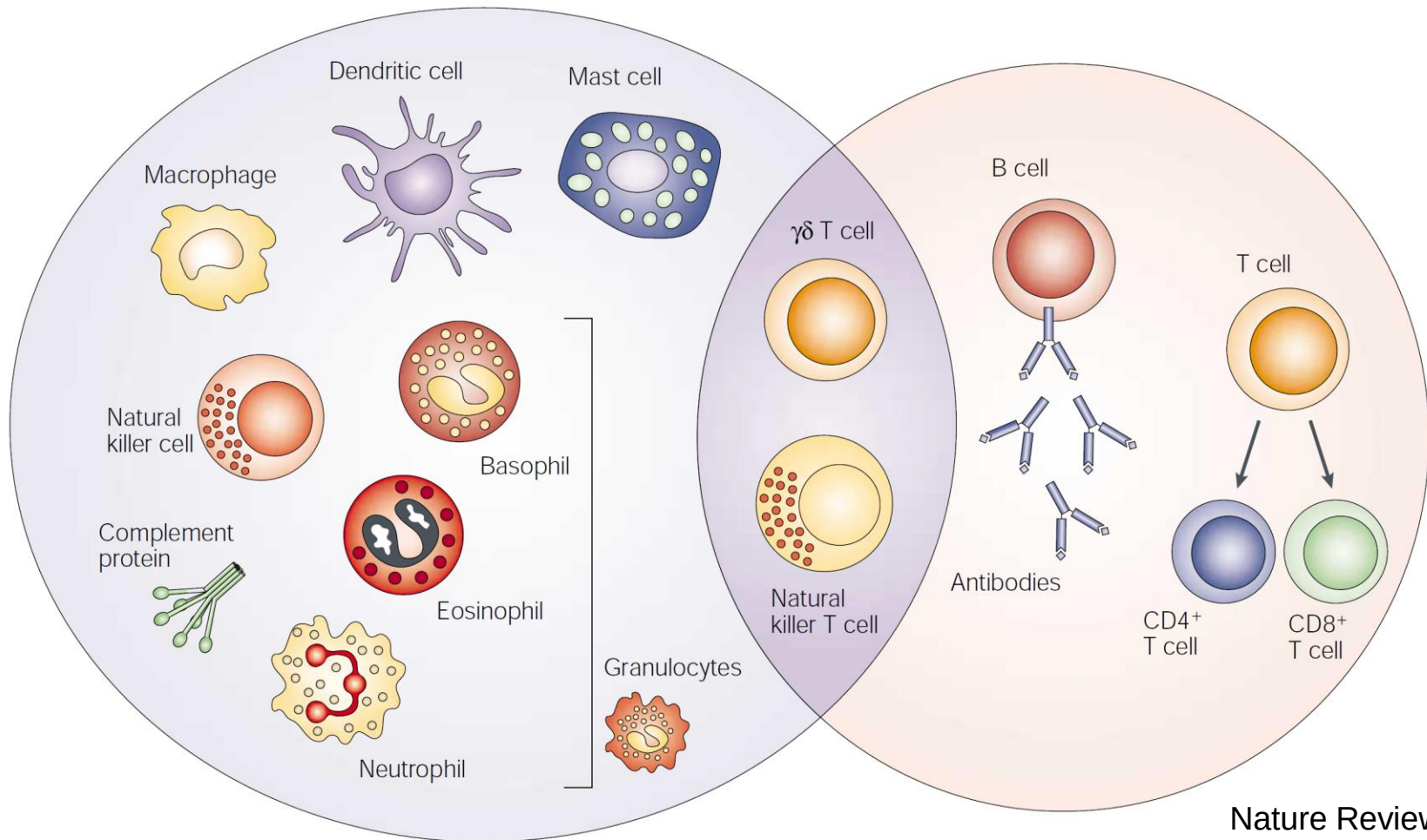
Components of the Immune System

Innate Immunity

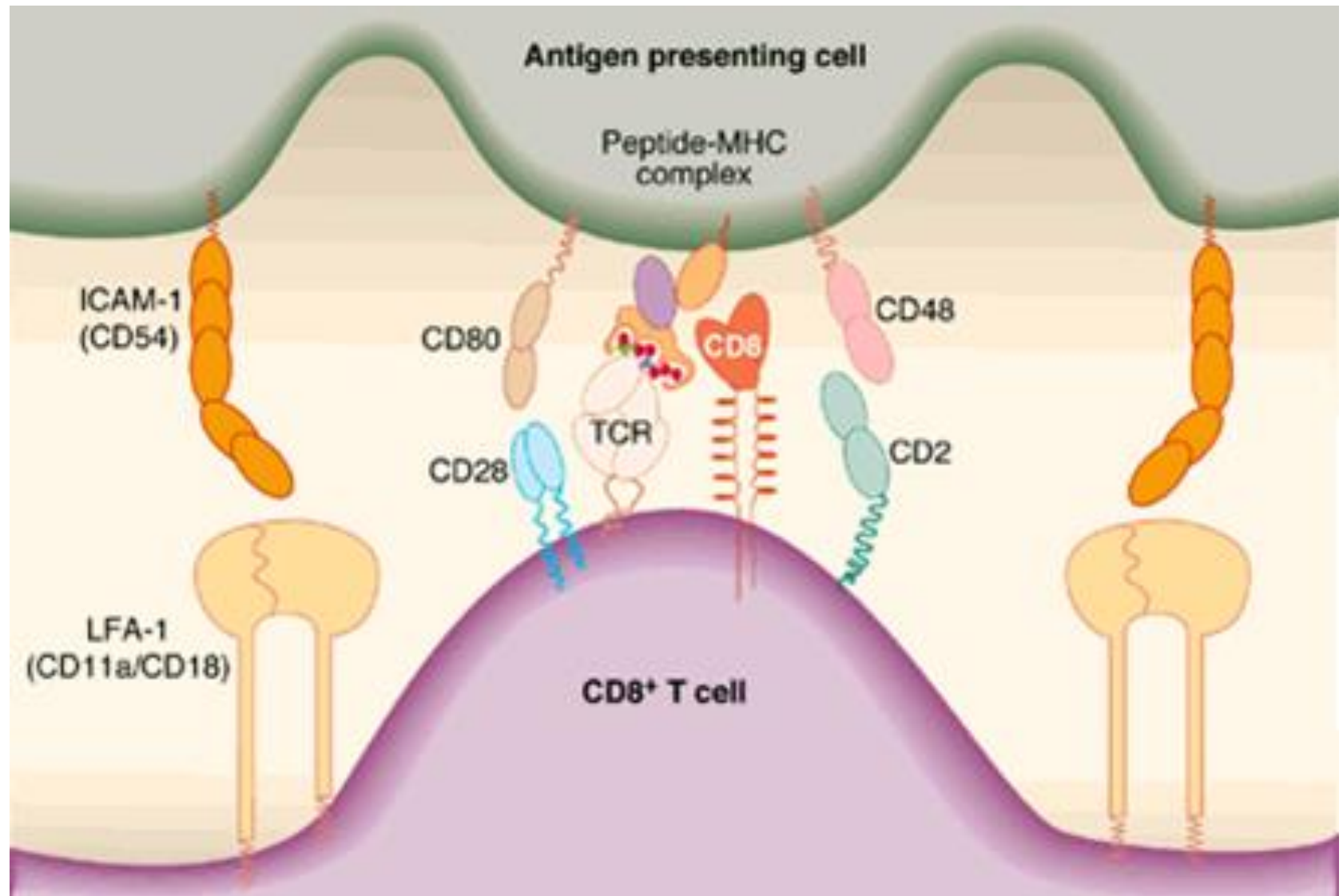
- Rapid Response
- Non-specific
- No Memory

Adaptive Immunity

- Slow Response
- Highly Specific
- Develop Memory



MHC Restriction & the Immunologic Synapse



Effective Immunotherapies for Metastatic Cutaneous Melanoma (CM)

Proliferation: Cytokines

Activate (release inhibition): Checkpoint
Blockade

Adoptive transfer: Autologous TIL

Effective Immunotherapies for Metastatic Cutaneous Melanoma (CM)

Proliferation: Cytokines

Activate (release inhibition): Checkpoint
Blockade

Adoptive transfer: Autologous TIL

Goal of Adoptive T Cell Transfer

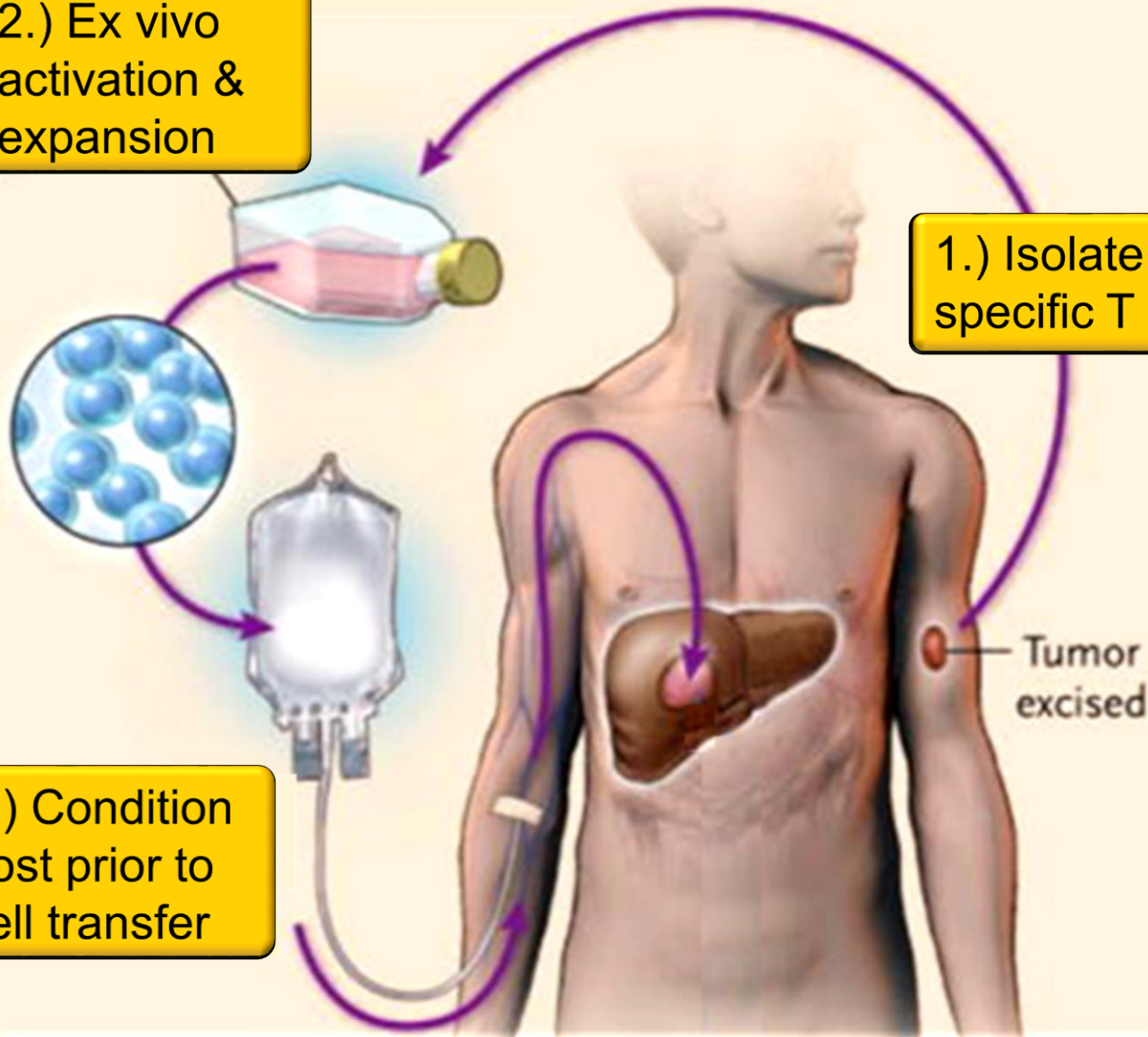
Physical repopulation of the host immune system with antigen specific T cells that:

1. Mediate potent effector function
(i.e. destroy tumor)
2. Persist and establish memory

2.) Ex vivo
activation &
expansion

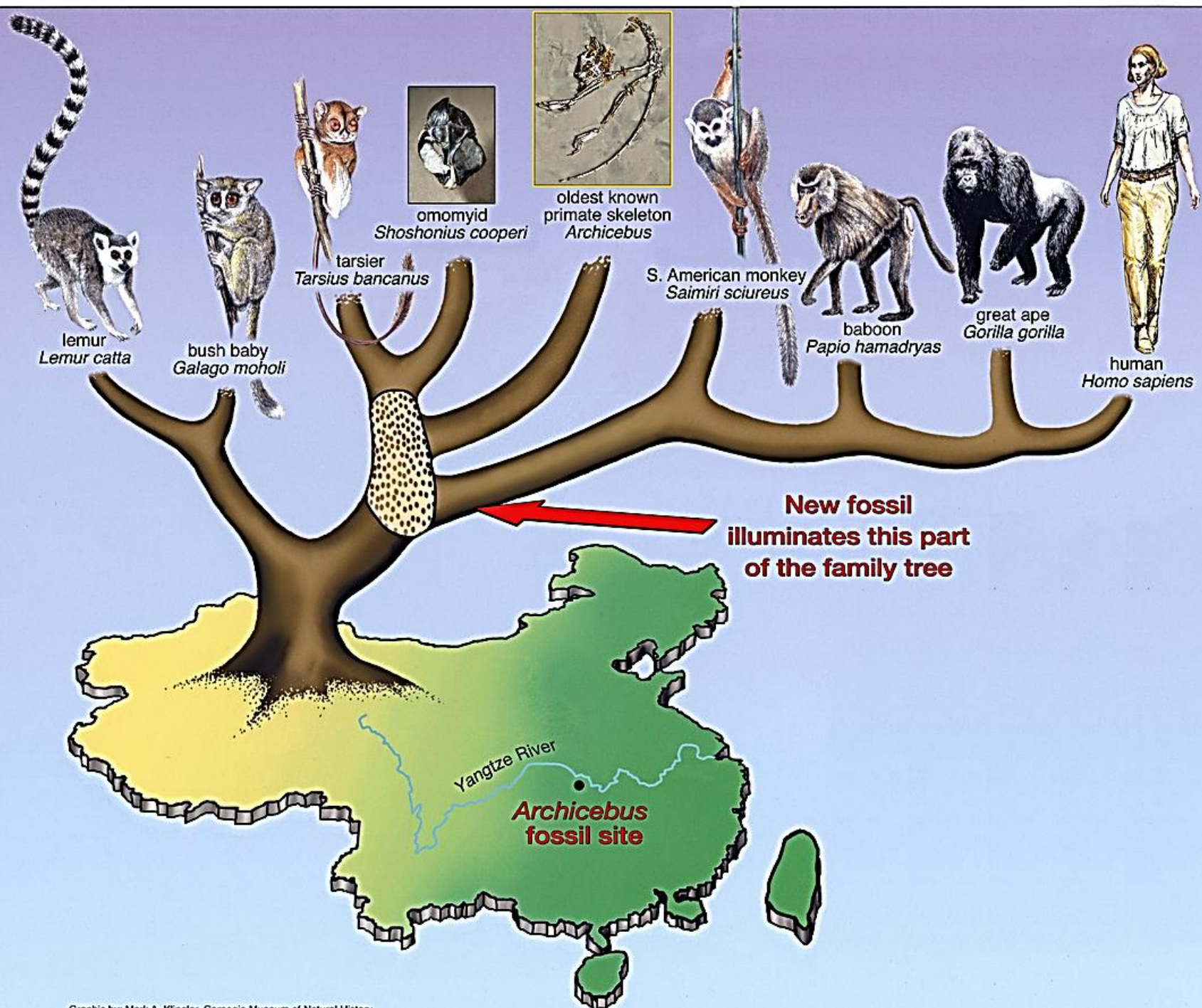
1.) Isolate tumor
specific T cells

3.) Condition
host prior to
cell transfer

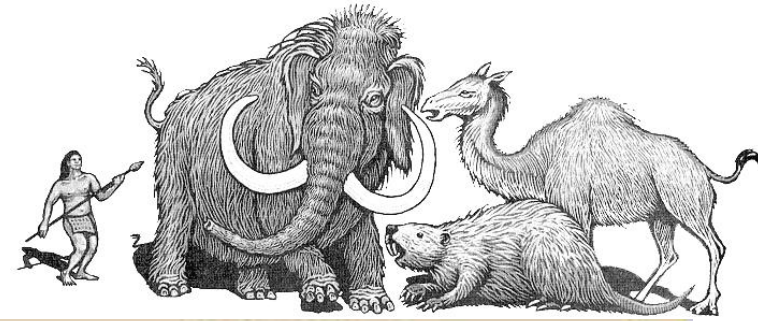


Why Lymphodeplete Prior to Cell Transfer?

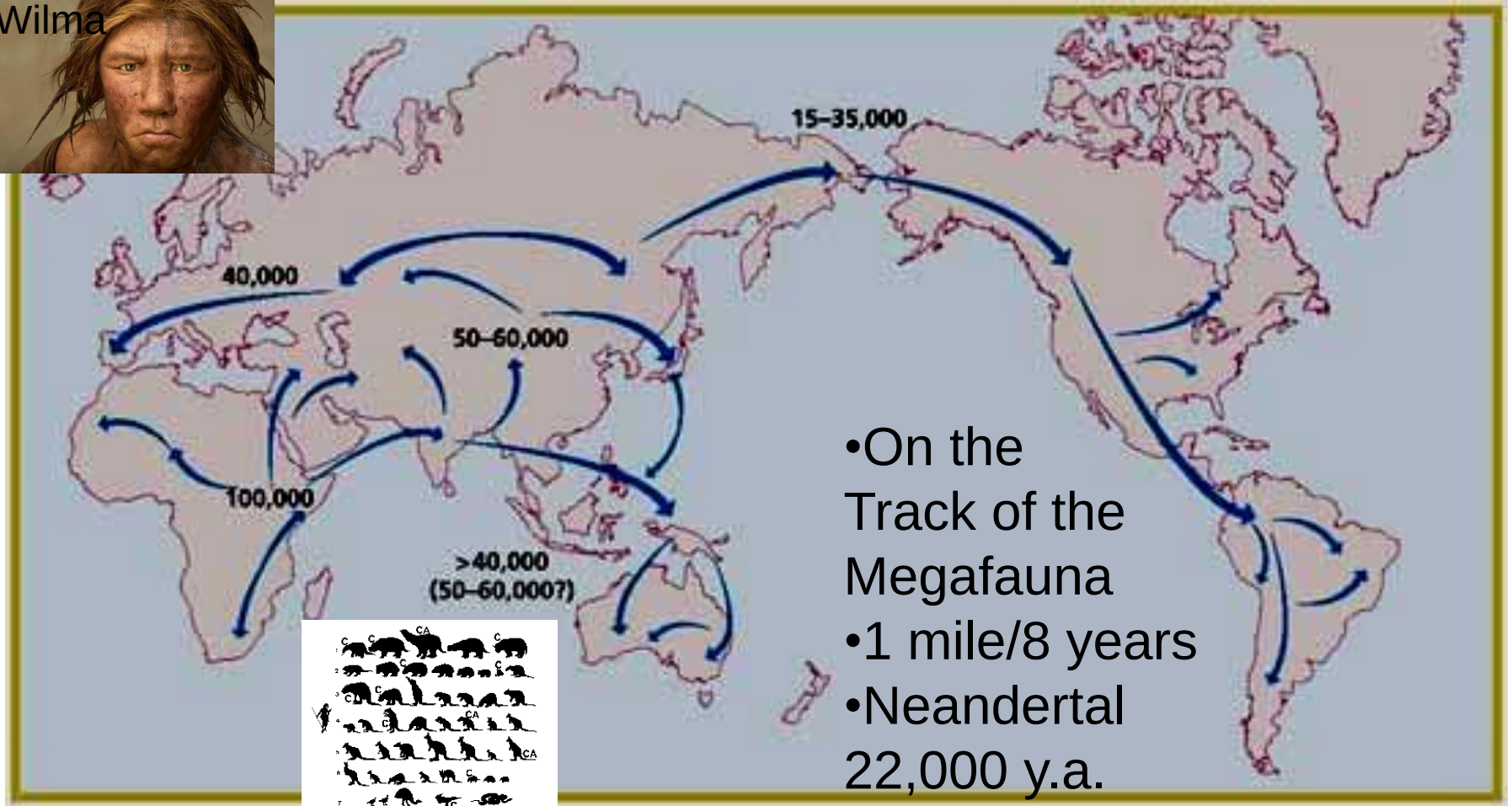
1. Eliminate suppressive cell populations (i.e. Tregs, MDSC, inhibitory macrophages)
2. Provide “space” for homeostatic expansion
3. Provide exposure to homeostatic cytokines (i.e. IL-15 and IL-7)



Out of Africa

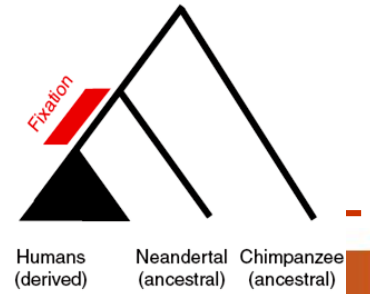


Wilma

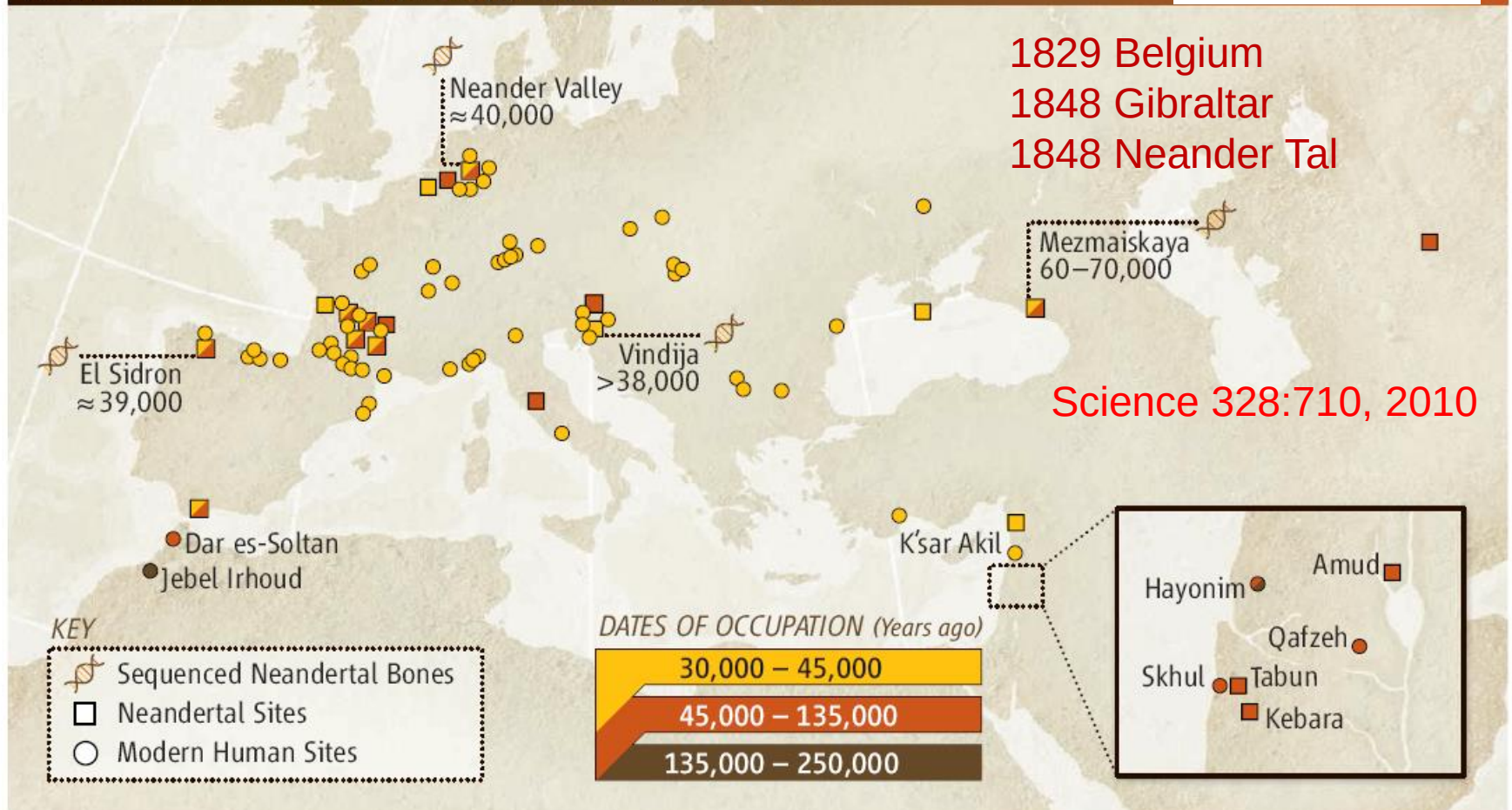


- On the Track of the Megafauna
- 1 mile/8 years
- Neandertal 22,000 y.a.

1-4% Neandertal In Humans



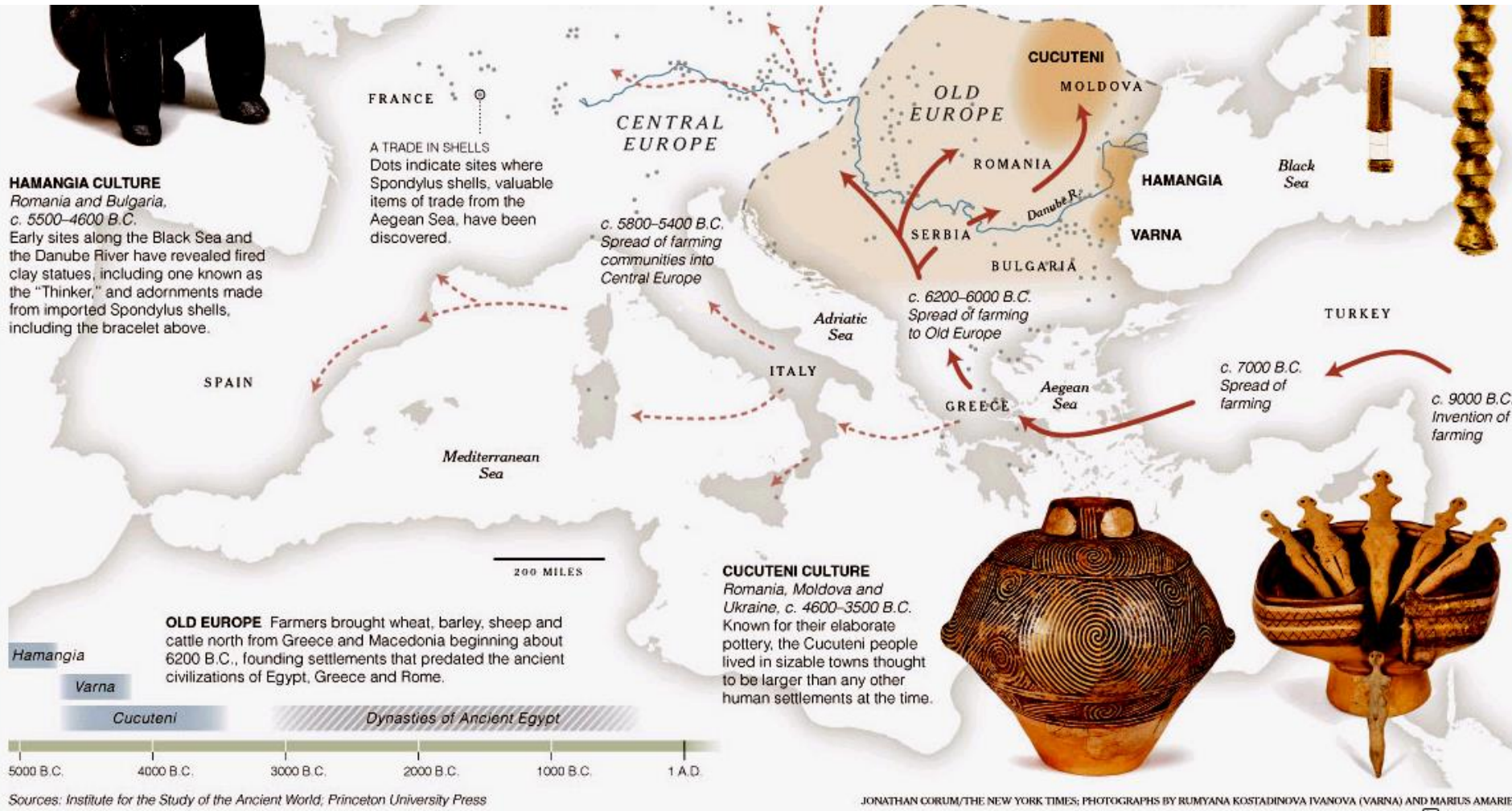
NEANDERTAL AND MODERN HUMAN OVERLAP



Points of contact. Archaeological data suggest that Neandertals and early modern humans may have overlapped early in the Middle East and later in Europe.

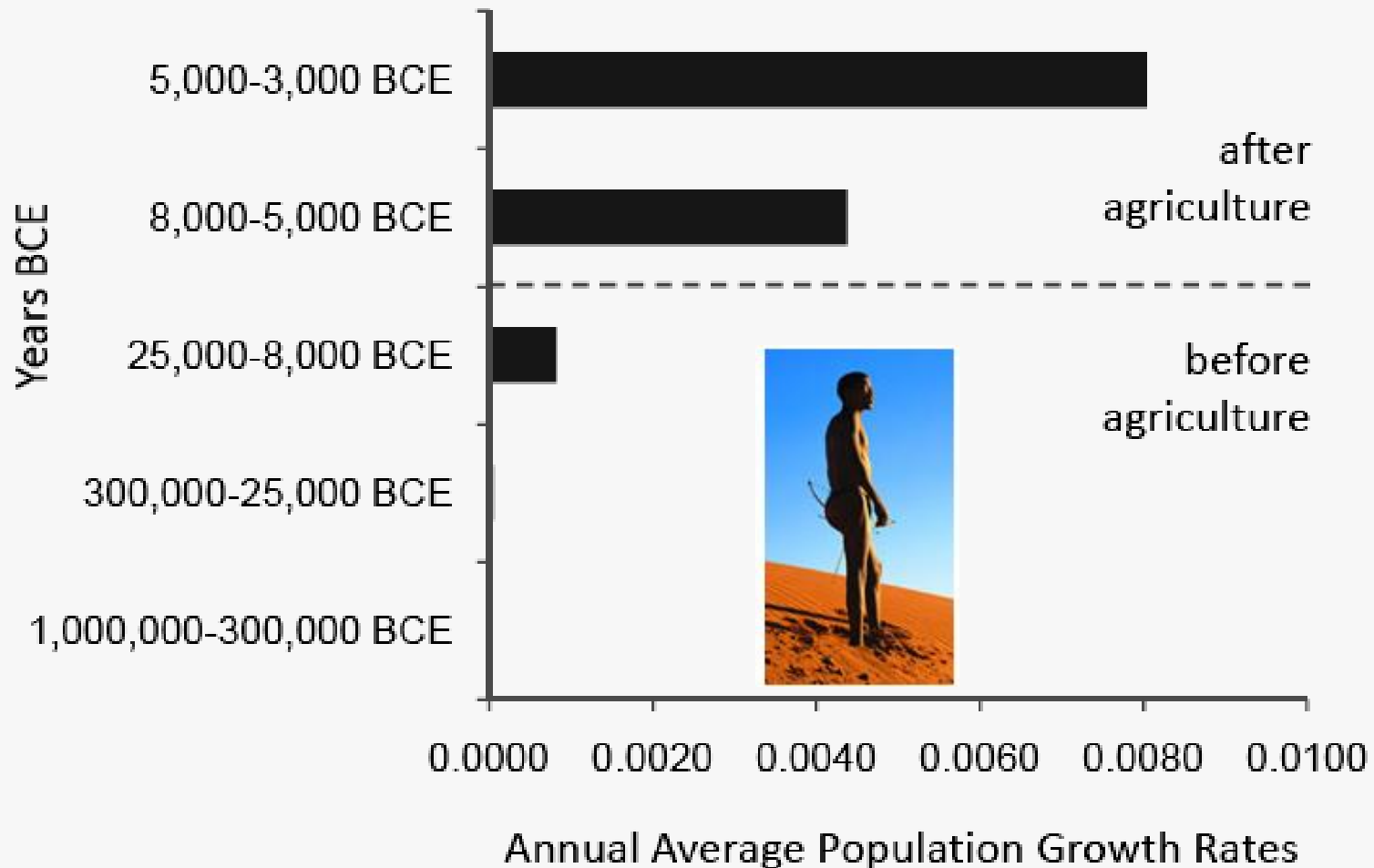
Farming Starts

New York Times December 1, 2009 Science Times/NYU



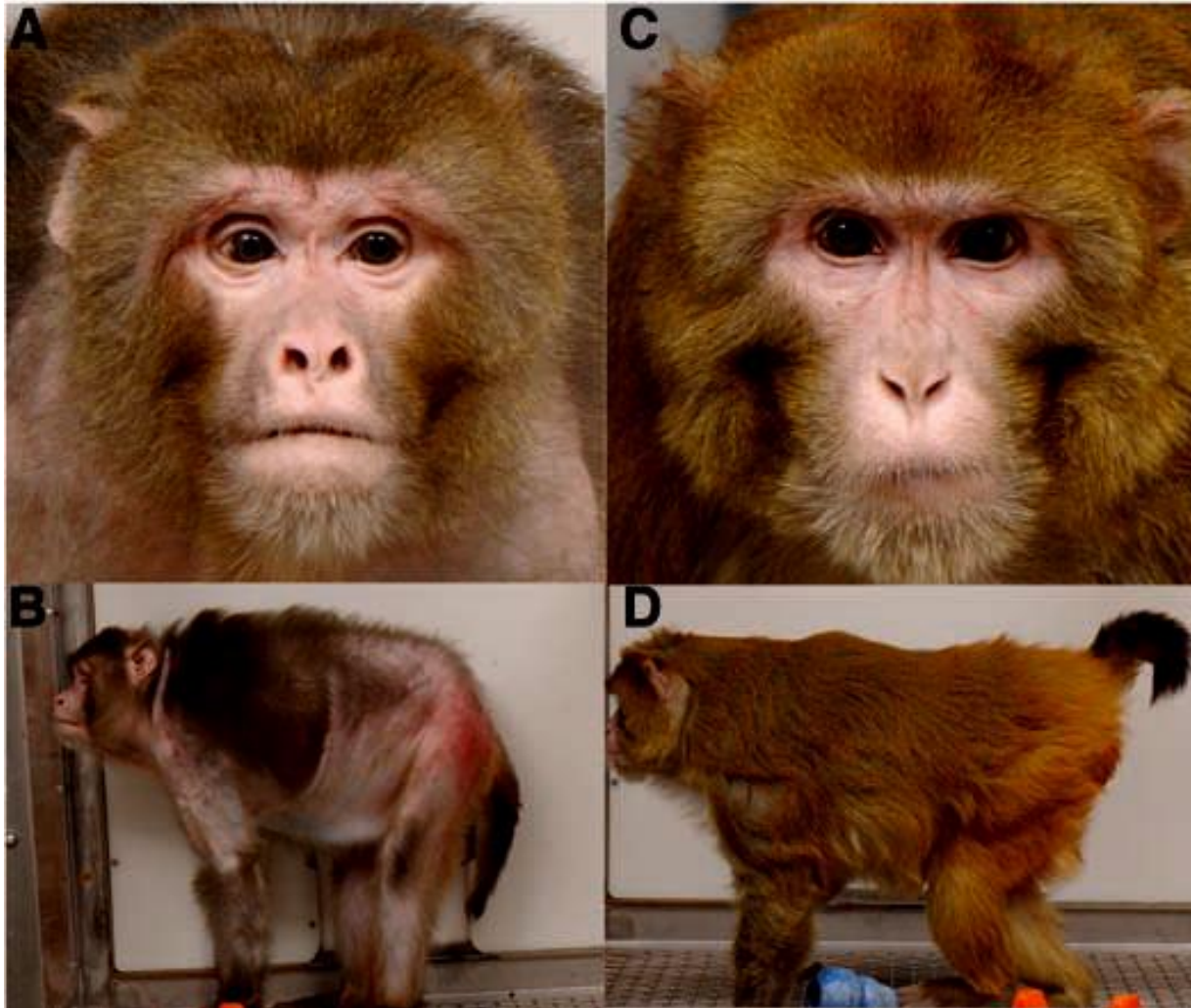
The Farmers Displaced/Replaced the Hunter-Gatherers

Population Growth Before and After Agriculture

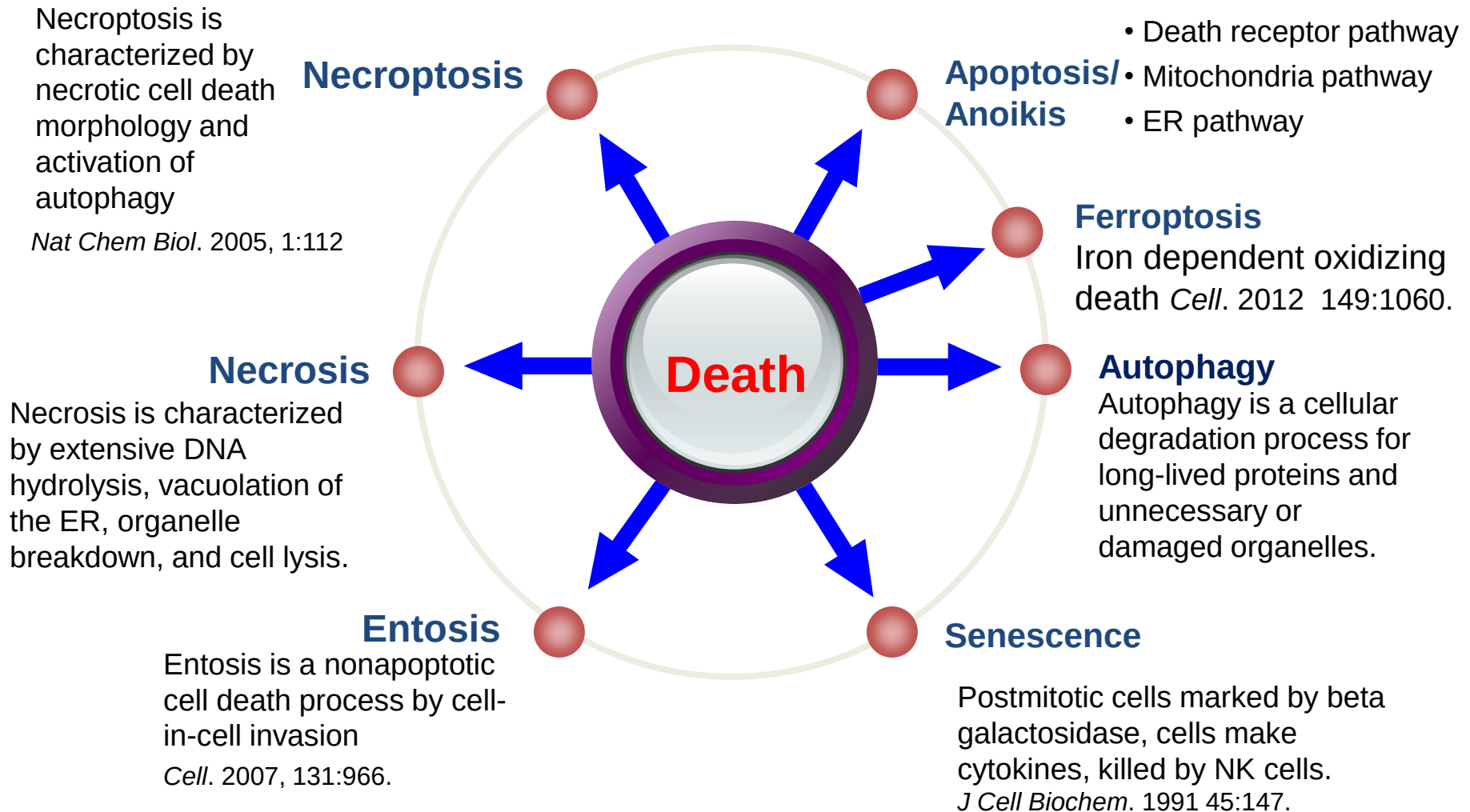


Source: Kremer (1993)

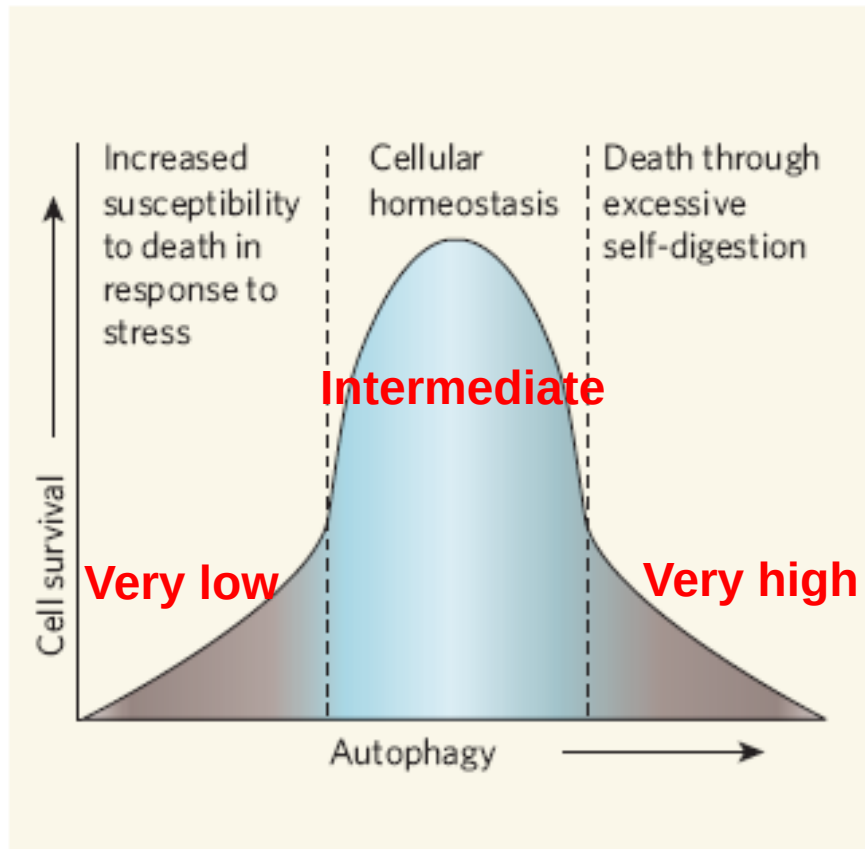
Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys



[Un]Natural History of Death



Relationship Between The Levels Of Autophagy And Cell Death



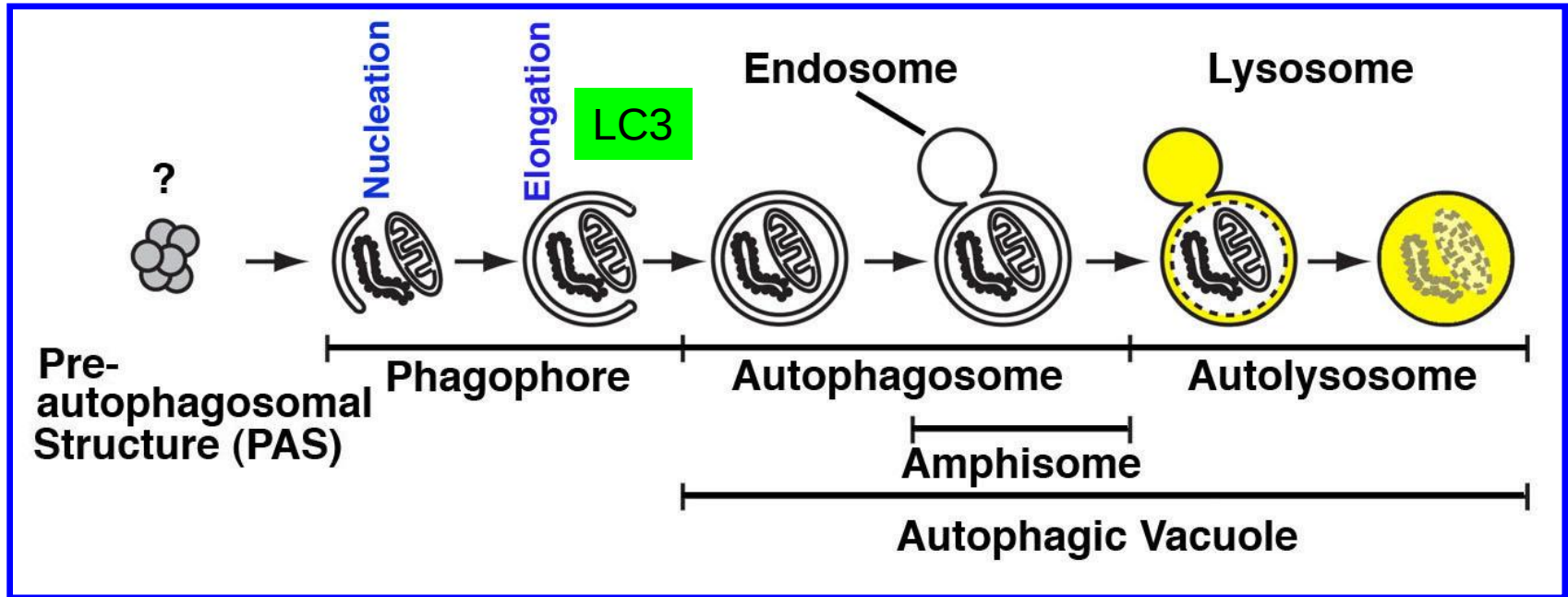
Nature **446**, 745-747 (12 April 2007)

Very low -- The absence of autophagy increases cell death during metabolic stress and on treatment with cytotoxic chemotherapeutic agents.

Intermediate -- Physiological levels of autophagy are essential for normal cellular homeostasis.

Very high -- excessive levels of autophagy promote cell death.

Mammalian Autophagy



Distinct autophagic phases:

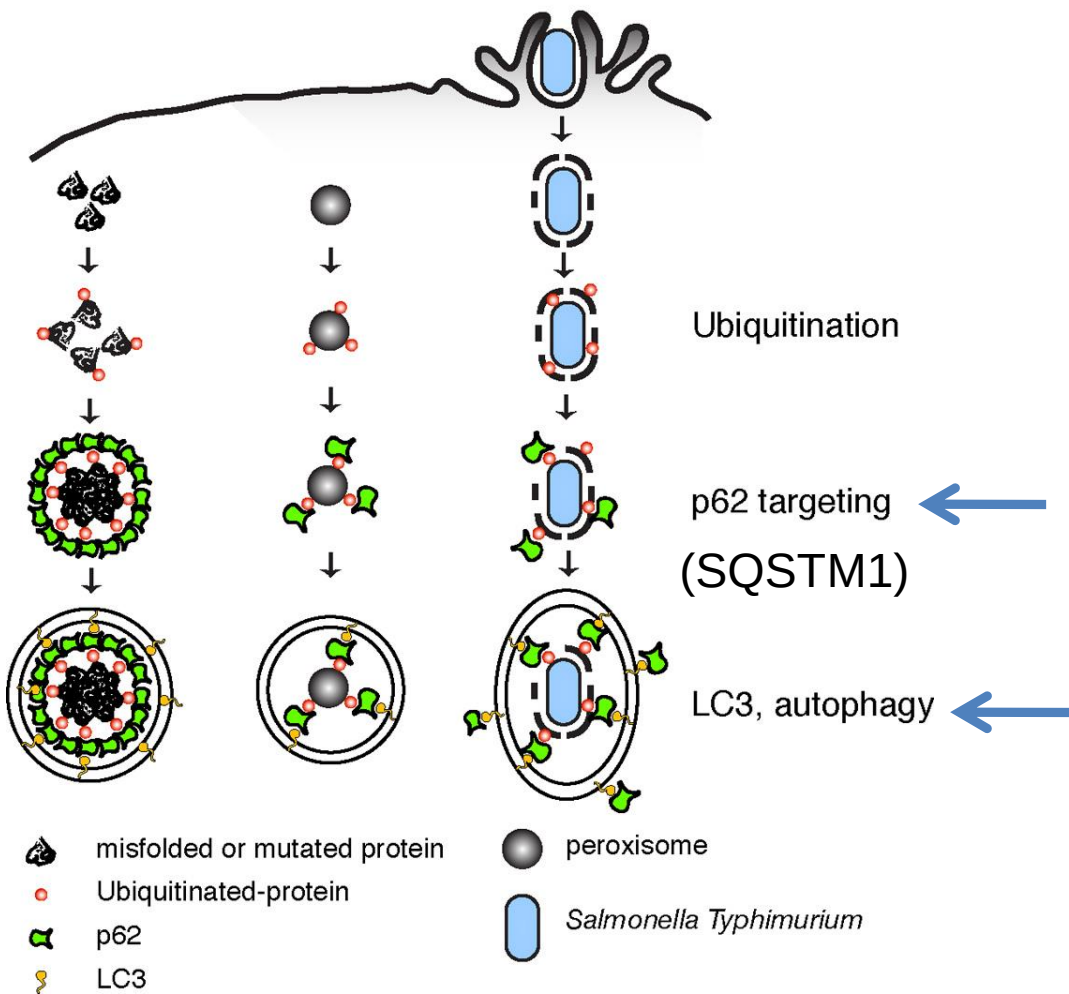
- I. Autophagosome formation — Sequestration
- II. Degradation
- III. Utilization — Provision of amino acids

Conserved Forms of Autophagy

aggrephagy

pexophagy

xenophagy



Ubiquitination

p62 targeting
(SQSTM1)

LC3, autophagy

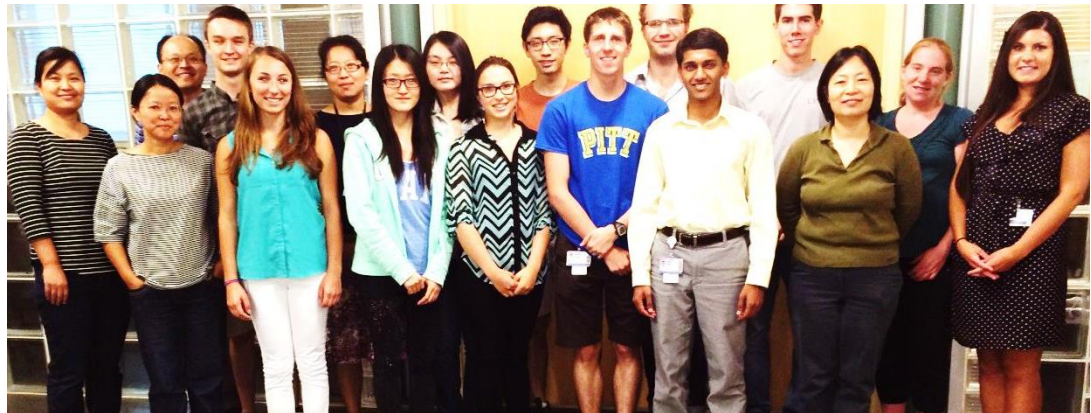
**molecular
markers for
autophagy**

Y Zheng et al
2009

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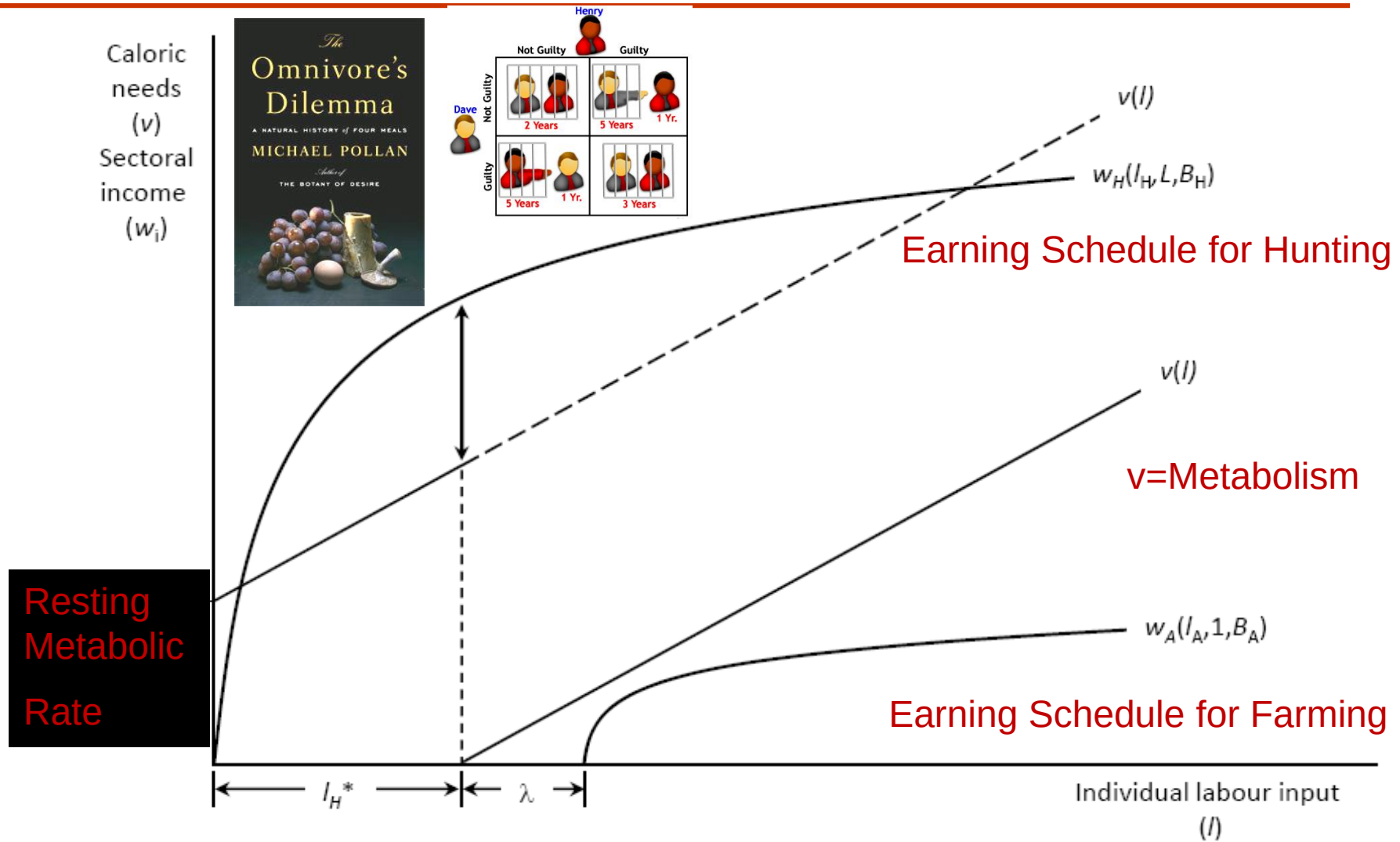


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- Anna Rubartelli, MD
- Marco Bianchi, PhD
- Angelika Bierhaus, PhD
- Kevin Tracey MD
- George Hoppe Ph.D



Malthusian Equilibrium Before Agriculture



"Why farm? Why give up the 20-hour work week and the fun of hunting in order to toil in the sun? Why work harder, for food less nutritious and a supply more capricious? Why invite famine, plague, pestilence and crowded living conditions?" (Harlan, *Crops and Man*, 1992) **THE PRISONERS DILEMMA**

DNA-RNA-Protein Size Matters?



- 3.2×10^9 Human Being

- 17.0×10^9 Onion



- 65.5×10^9 Broad-footed salamander

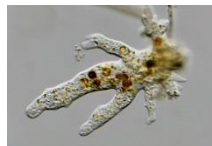
- 132.0×10^9 African Lungfish

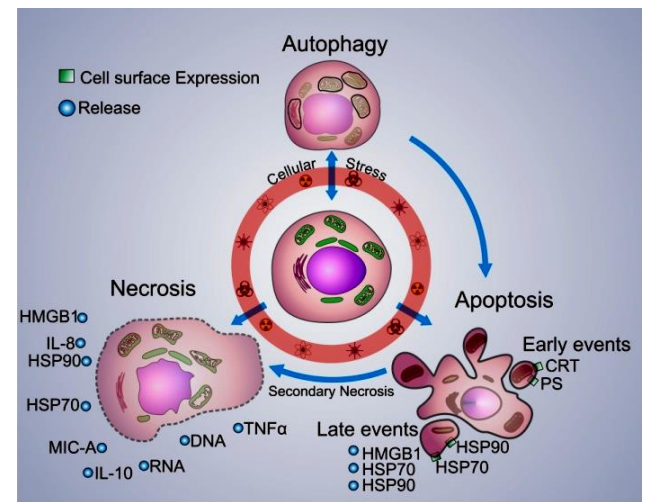


- 149×10^9 Paris Japonica Flower



- 670×10^9 *Amoeba dubia*=*Polychaos dubium*

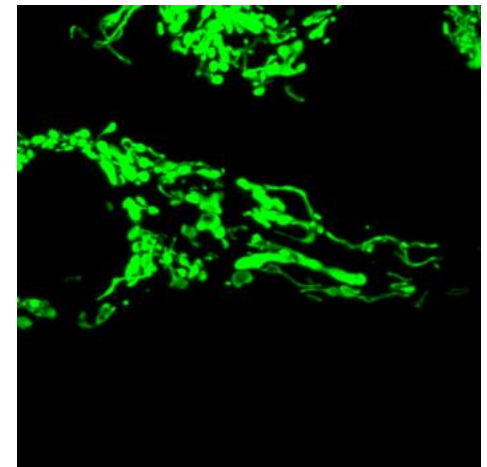




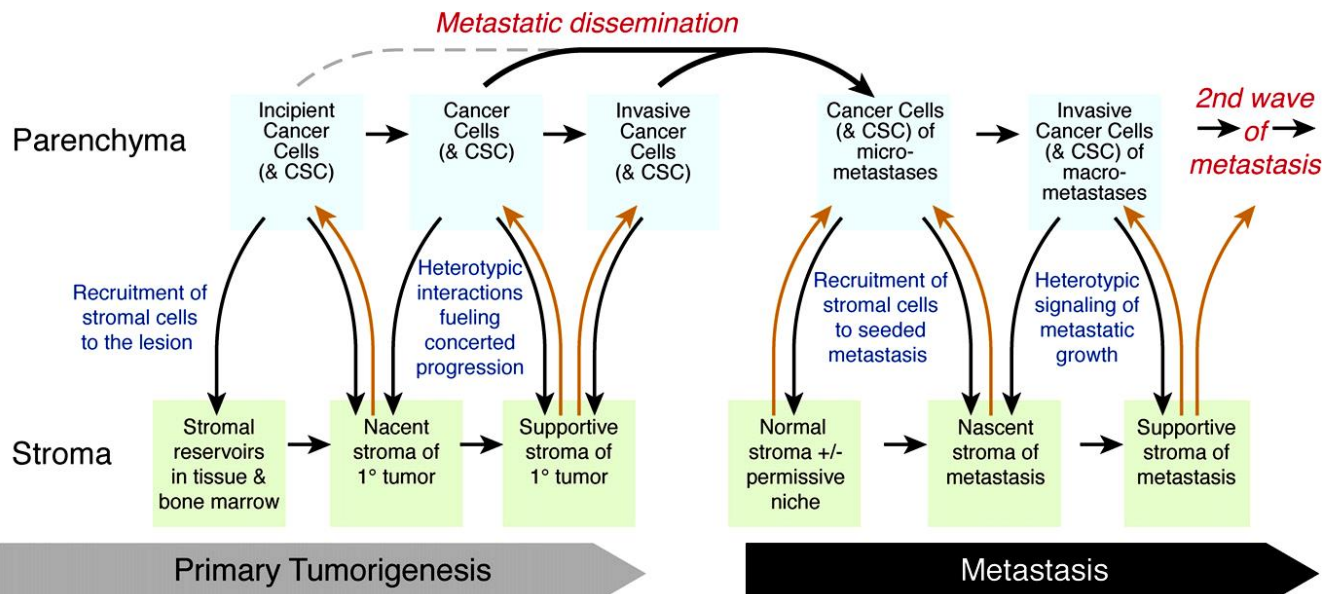
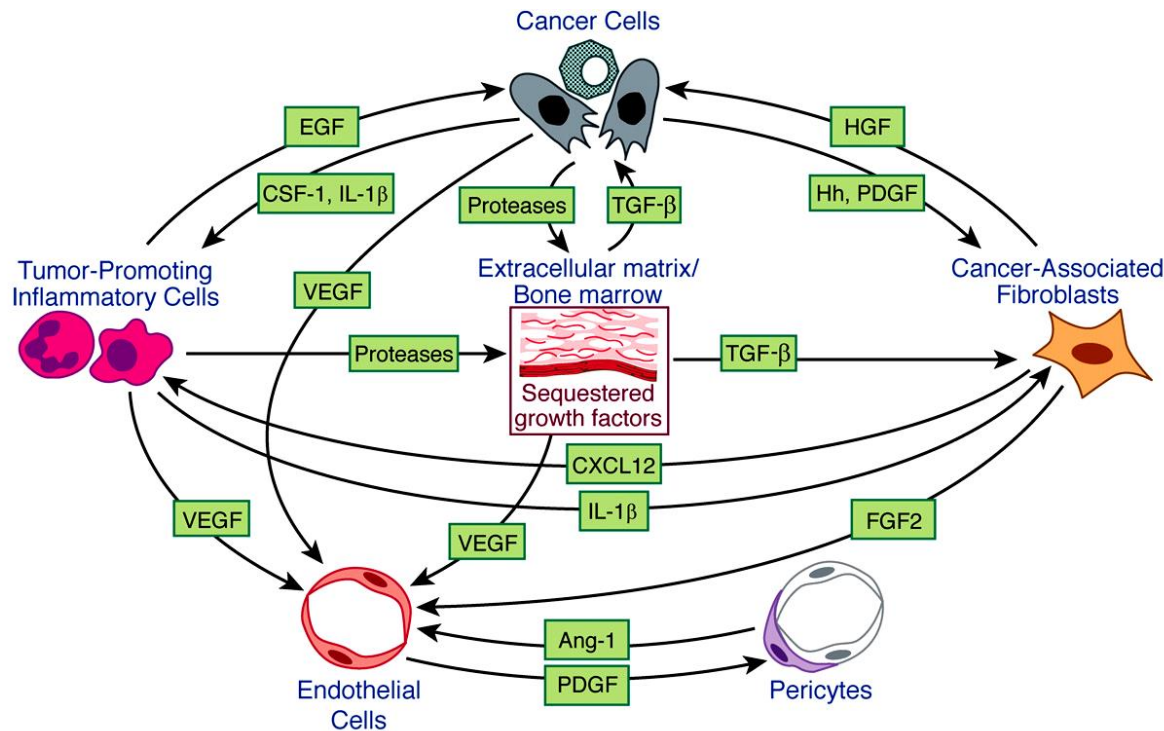
Cancer is a Disorder of Genes, Cell Death, Metabolism, and Immunity

History of Life
History of Death
Apoptosis/Autophagy
History of SITC/iSBTC,
SBT

Michael T. Lotze, MD
Vice Chair Research
Department of Surgery



Signaling Interactions in the Tumor Microenvironment during Malignant Progression



Hanahan D,
Weinberg R.
Hallmarks of
Cancer: The
Next
Generation.
Cell 144,
March 4,
2011