Immunity Summoned:

Fever's Journey to Immunotherapy

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Disclosures

I have no conflicts of interest to disclose in relation to this presentation

MY FEVER & Immuno-therapy BIO

- B.Sc. in Biological Sciences
- Integrative Oncology (ND) practice since 2000
- Licensed in BC, Canada and Washington State, USA
- Fellow of the American Board of Naturopathic Oncology (FABNO) since 2007
- Clinical Hyperthermia (HT) training (Europe,++Germany)
- Published an 8-year observational study on HT
- Thousands of fever-range whole body HT treatments
- > 20 years working with immunotherapeutics

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Today's AGENDA

- Body Temperature and Thermal Regulation Basics
- History of thermometry
- What is fever & who builds fevers?
- What happens if a fever is suppressed in animals & humans?
- History of fever therapy & the "afebrile diathesis"
- Immunotherapy Timeline to Today
- Immunotherapy today – Review 4 Major Classes of Drugs
- Naturopathic Immunotherapy
- My personal hypothesis & public service announcement

Body Temperature

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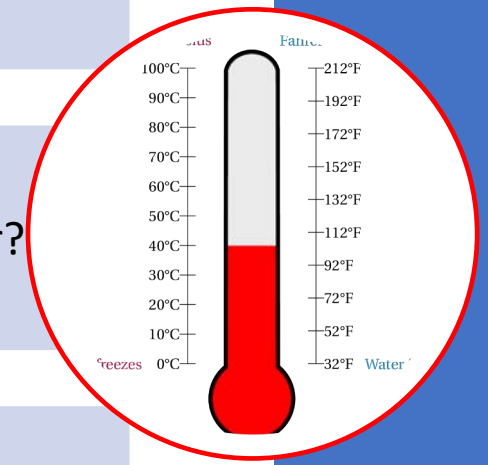
Why does body temperature matter?

How and why do we regulate body temperature?



What is a Fever?

How and why do we build a fever?

***Special Acknowledgements:**

Mathew J. Kluger, PhD, Philip A. Mackowiak, MD, and Paul Young, MD

Human Thermal Regulation Basics

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Average temperature on earth

16 ℃

Average human core body temperature is

36 -36.5 ℃

1800 kcal/day

The “up to” daily requirement in low temperatures

1 ℃ increase = 10 to 12.5% increase to caloric demand

American Alligator (20-25℃) daily energy expenditure:

60kcal/day

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Why are we so hot?

All thermoregulators on earth maintain between 35°C to 42°C

High temperature is necessary for our biochemical reactions, which are what make our physiology work

Many biochemical reactions increase their reaction rate 2 to 3-fold over a 10°C change (referred to a a Q_{10})

In 1800's, Arrhenius proposed biochemical reactions increase "logarithmically" with temperature to an optimal max point

Beyond this optimal max point, reactions decrease

In fact, proteins start to denature at 45°C

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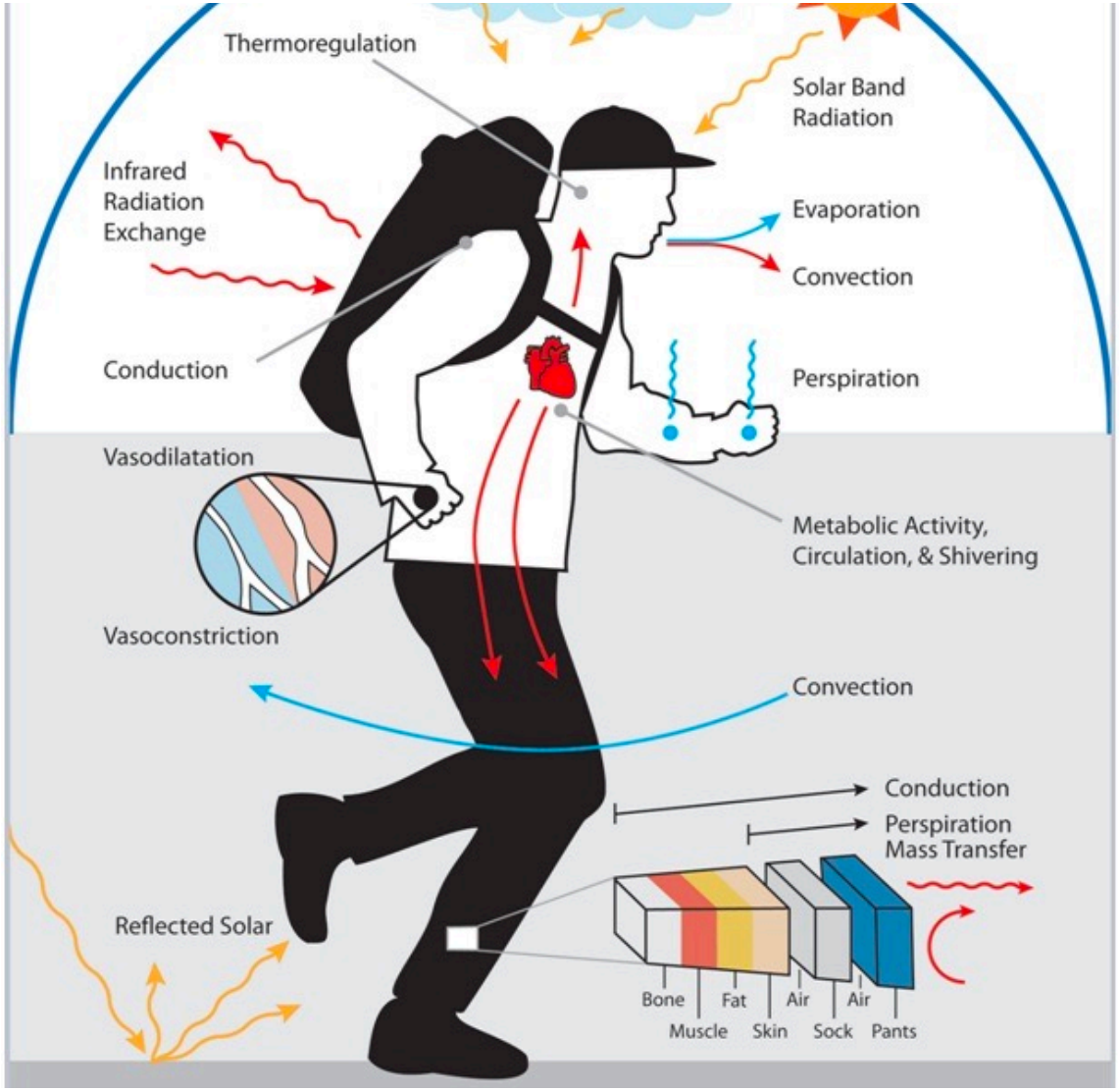
Heat Regulation & Our Earthly Environment

- CONDUCTION
- CONVECTION
- RADIATION
- EVAPORATION



Thermoregulatory Reflex

1. Sensors

Skin

Nerves (non-myelinated)

Hypothalamus

2. Integrators

Hypothalamus (POAH)

Spinal cord

3. Effectors

Physiological changes - shivering, vasoconstriction/dilation, sweating, panting

Behavioral changes - moving into sun/shade, bundling, stripping, etc.

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History of the Thermometer

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Sanctorius invented the first thermometer in **1611**

Sanctorius documented temperature differences between those in health & those with illness

Sanctorius even used temperature to estimate status of infection

Late 1600's Ranildini proposed melting point of ice & boiling point of water as the ends of a temperature scale

Early 1700's Farenheit scale was created, and sometime later the Celsius scale.

Since **mid-1700's**, temperature scales and thermometers have been available

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Wunderluch's Medical Thermometry

100 years later, in **1861**, Louis Pasteur published his Germ Theory

In **1871** Wunderlich published *"Medical Thermometry"*

Promoted thermometry as an objective, reproducible, and accurate method of measuring something that can be expressed numerically

Measured temperature rigorously and determined that "healthy temperature"

< 38 °C and is > than that in those with illness

SET-POINT CONCEPT
(Snell & Atkins 1968)

1968 when Snell and Atkins proposed the concept of body temperature

Normothermic

Temp = Set point

Hypothermic

Temp < Set point

Hyperthermic

Temperature > Set point

Fever

Temperature + **Set Point higher** than normothermia

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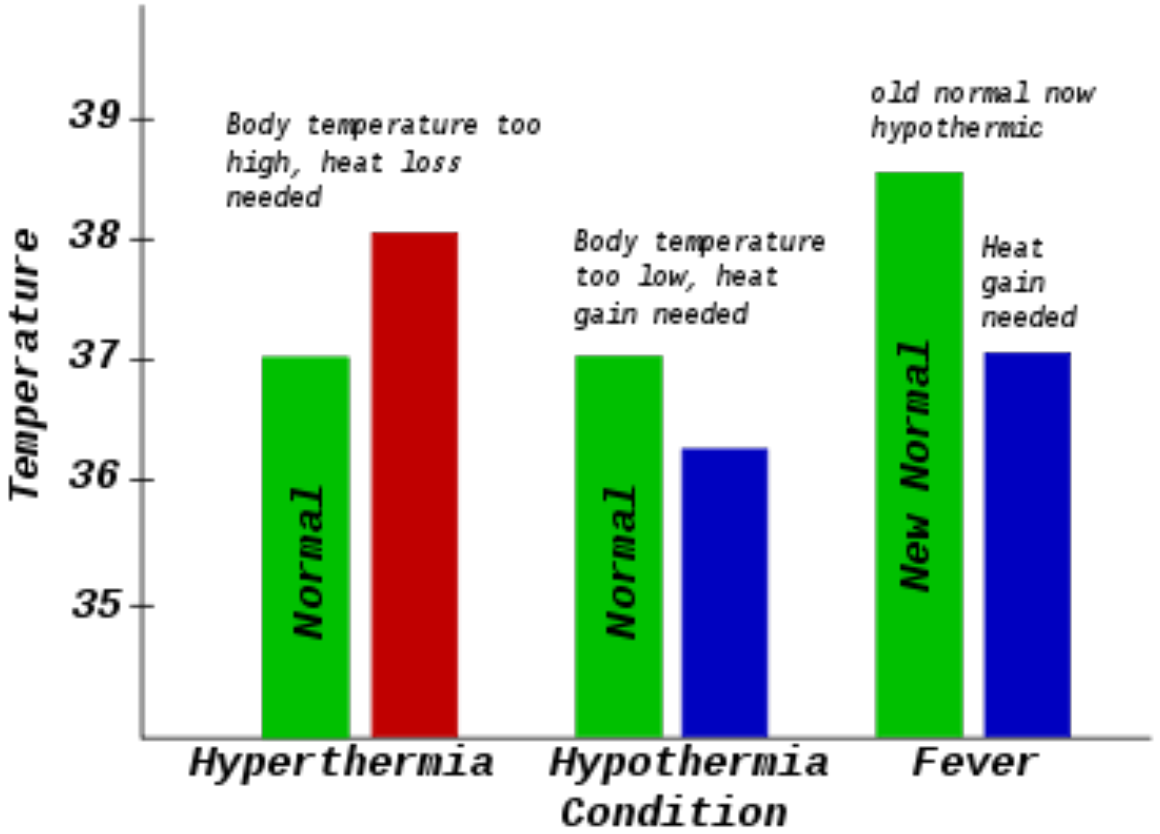
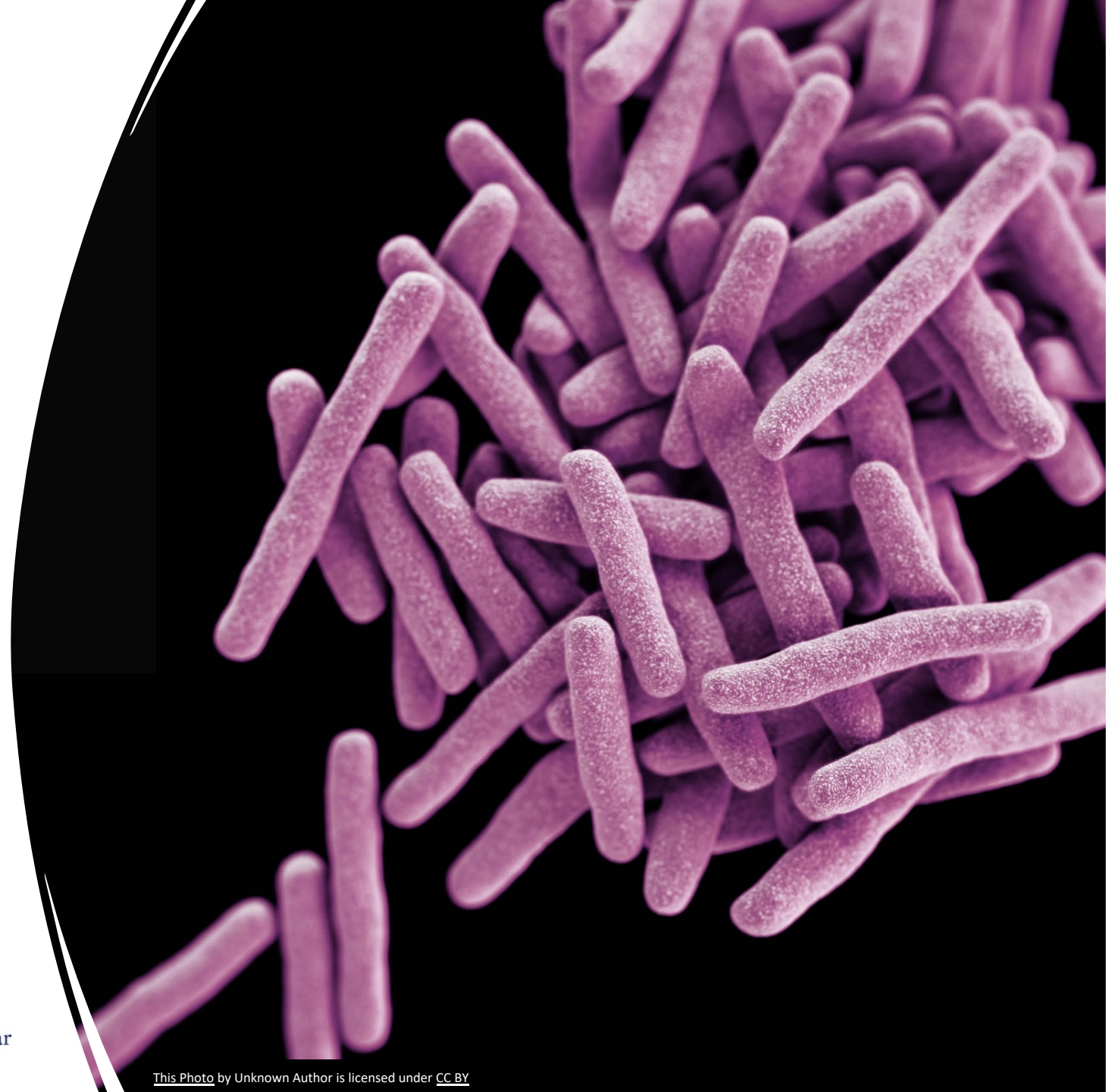


What Causes Fever?

- Infections
- Malignancies
- Traumas
- Surgery
- Heat exhaustion
- Inflammatory Conditions
- Autoimmune conditions
- Severe allergies
- Unknown Causes



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What Does Fever Accomplish?

- Kills microorganisms (bacteria, viruses, fungi, and parasites)
- Increases bactericidal action of neutrophils and other WBCs thereby decreasing bacterial growth
- Increases leukocyte production and function/mobility/action
- Induces behavioral changes like aches/pain, fatigue, sleepiness, and anorexia to conserve energy
- Increases acute phase protein synthesis to create inflammatory response (CRP, ferritin, albumin, etc.)
- Decreases serum iron to reduce availability to pathogens (“nutritional immunity”)

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Common Symptoms of Fever

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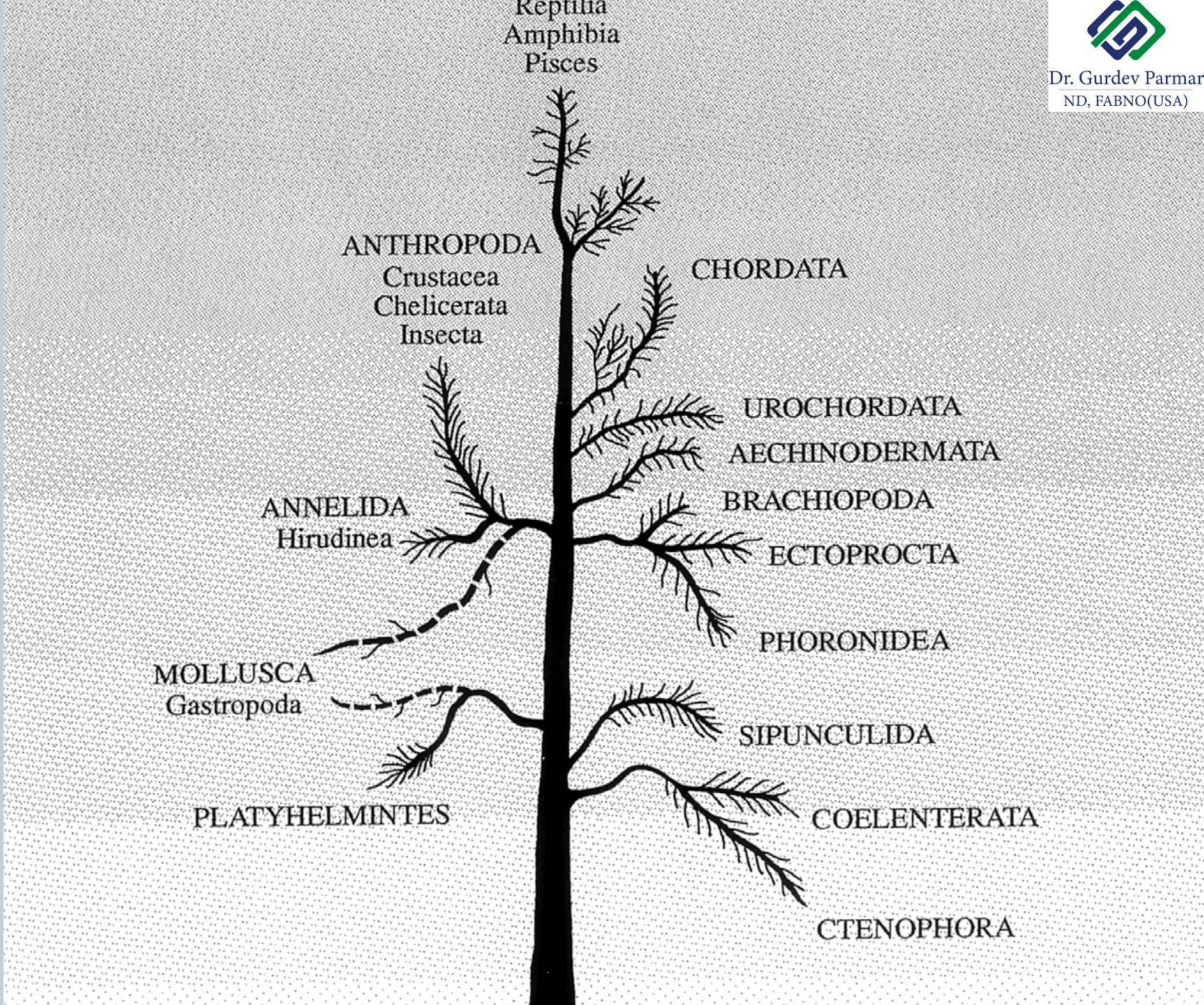
- A raised body temperature set-point of 2-4 ℃ (38.5-40.5 ℃)
- Body Aches & pains (stay put)
- Headache (vasodilation with peripheral vasoconstriction)
- Shivering (skeletal muscle heat production)
- Sweating (skin cooling)
- Fatigue & somnolence (to preserve energy)
- Lack of appetite (to preserve energy)
- Dehydration (increased demand)

Who Builds Fever?

Febrile response documented in the phyla Vertebrata, Arthropoda, and Annelida

They diverged over 4 million years ago!

Mackowiak PA. Temperature regulation and the pathogenesis of fever. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and practice of infectious diseases. 5th ed. Philadelphia: Churchill Livingstone, 2000: 604–22.



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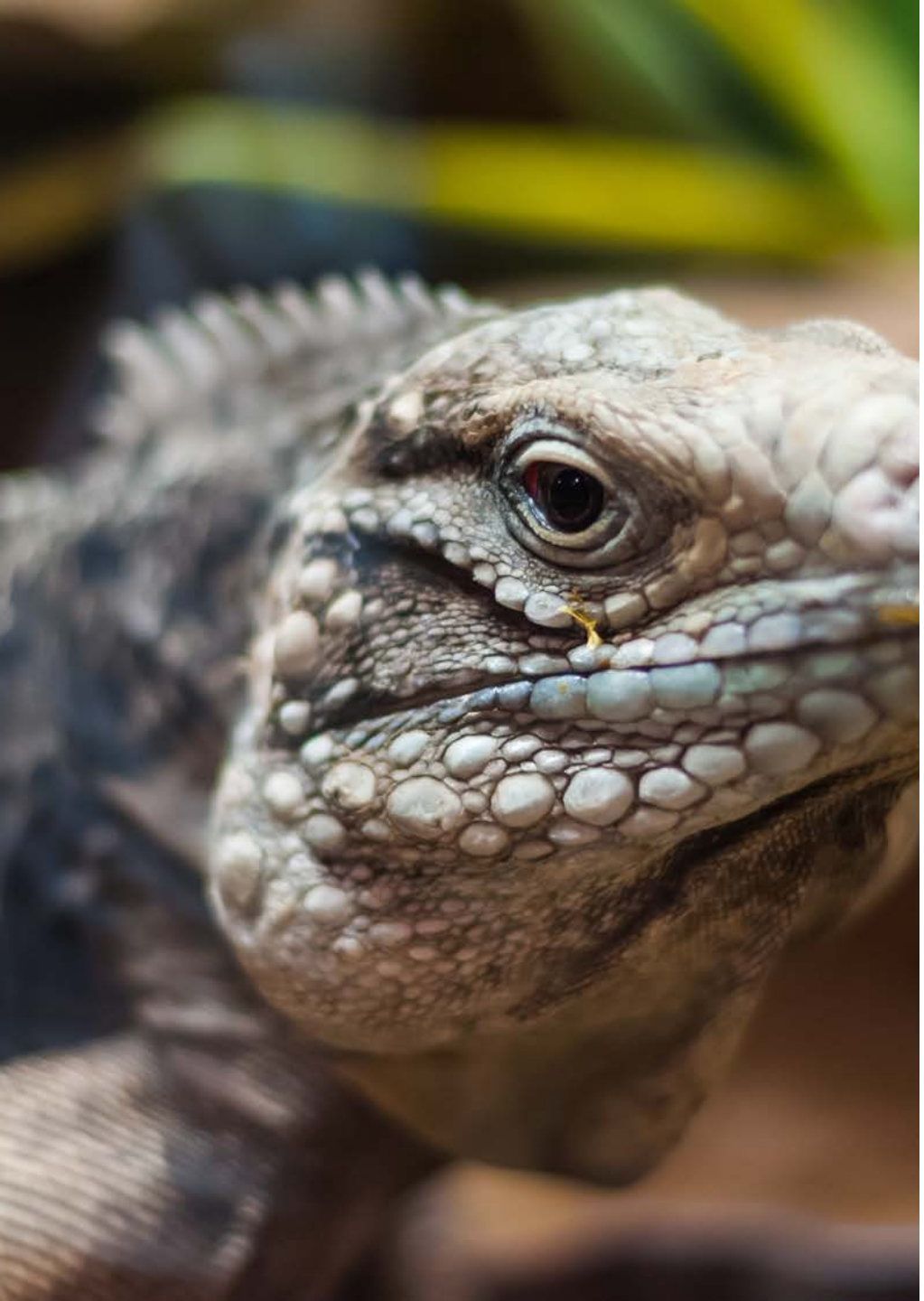

Fever & Evolution

- Fever is a mechanism that is hundreds of millions years old!
- Found in:
  - Mammals (175 million years)
  - Birds (180 million years)
  - Reptiles (280 million years)
  - Amphibians (375 million years)
  - Cartilaginous fish (400 million years)
  - Bony fish (400 million years)

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Desert Iguanas

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Infected desert iguanas with *Aeromonas hydrophila*

Gave them the opportunity to seek heat via sunlamps

All but one sought warmth to raise temperature. The one iguana that did not heat itself was the one that died

Next, injected the iguanas with *Aeromonas* and then gave them antipyretics

The iguanas able to mount a fever despite the antipyretic were the only ones that survived

Kluger MJ, Ringler DH, Anver MR. Fever and survival. Science 1975;188:166-8.

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Goldfish

- Fever significantly enhances survival of *Carassius auratus*, or goldfish
- Goldfish were injected with *Aeromonas hydrophila*
- The mean febrile temperature rise was 4.8°C
- Goldfish in febrile temperature of 30.5°C had 84% survival versus 24% at 25.5°C
- **Survival value of fever in fish.** JERRY B. COVERT & WILLIAM W. REYNOLDS . *Nature* **volume 267**, pages43–45(1977)

New Zealand White Rabbits

- Rabbits injected IV with bacteria *Pasteurella multicoda* and either sodium salicylate or saline
- Fever temperatures in salicylate group were reduced by 50%
- 100% of the rabbits in the salicylate group died
- Only 29% of the control group

Brain Research Bulletin. Antipyresis: Its Effect on Mortality Rate of Bacterially Infected Rabbits L. K. VAUGHN, W. L. VEALE AND K. E. COOPER. 1979

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Honeybees

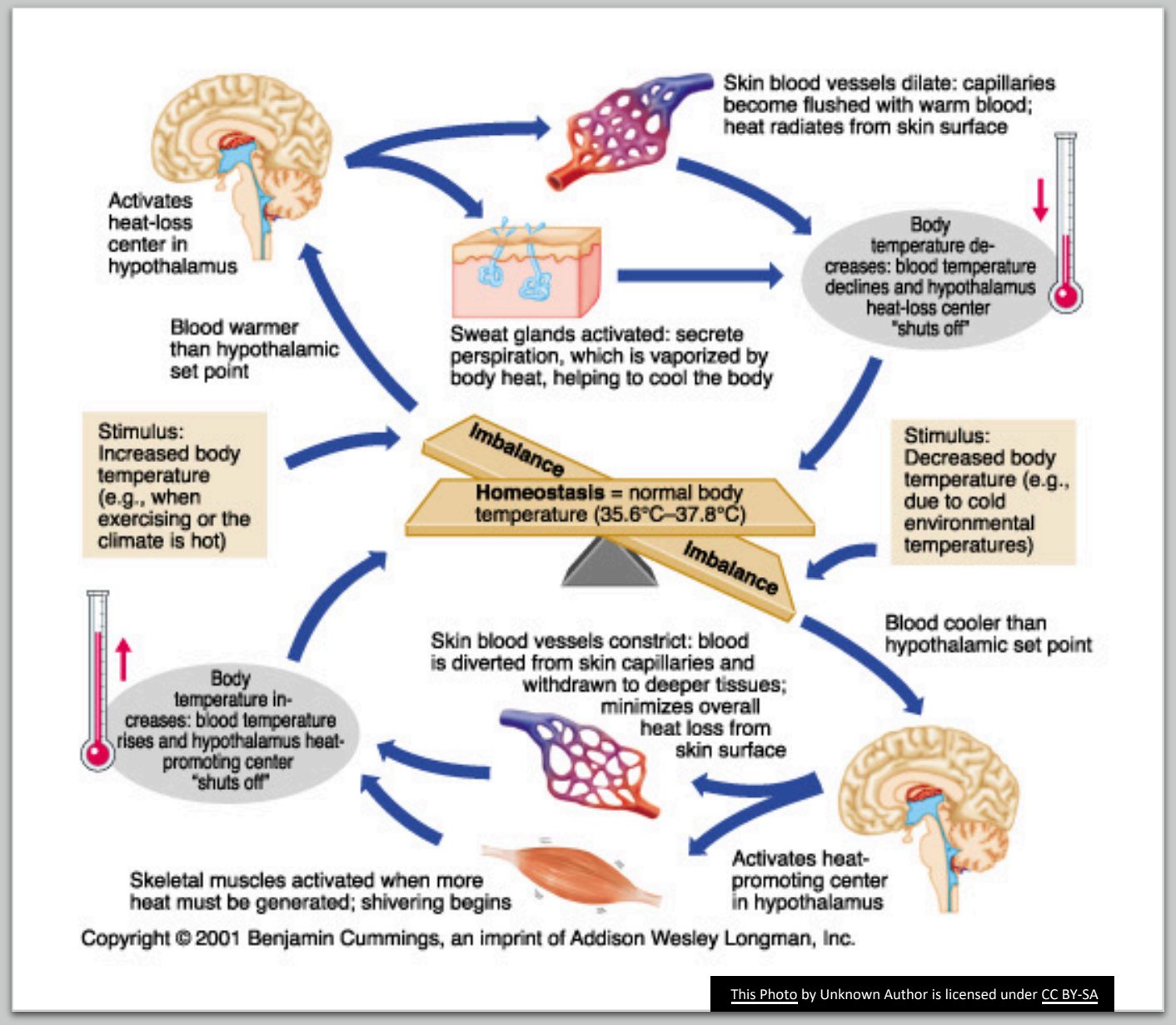
- Honeybees manipulate hive temperature in response to presence of pathogens
- The fungus that causes “chalkbrood” triggers “social fever” (Stark et al, 2000)
- Bees “vibrate” together to raise temperature of a fungally-infected hive to save larvae from infection
- Raising the temperature of the hive by about 4°C with this behavioural “social fever”

Impact of Food Availability, Pathogen Exposure, and Genetic Diversity on Thermoregulation in Honey Bees (*Apis mellifera*). M. Simone-Finstrom, B. Foo, et al. *Journal of Insect Behavior* volume 27, pages527–539(2014)

What happens during Fever?

- **Co-Ordinated Set of Changes:**

1. Behavioral changes
2. Diaphoresis (sweating)
3. Vasodilation at core
4. Vasoconstriction at surface
5. Shivering (Ach)



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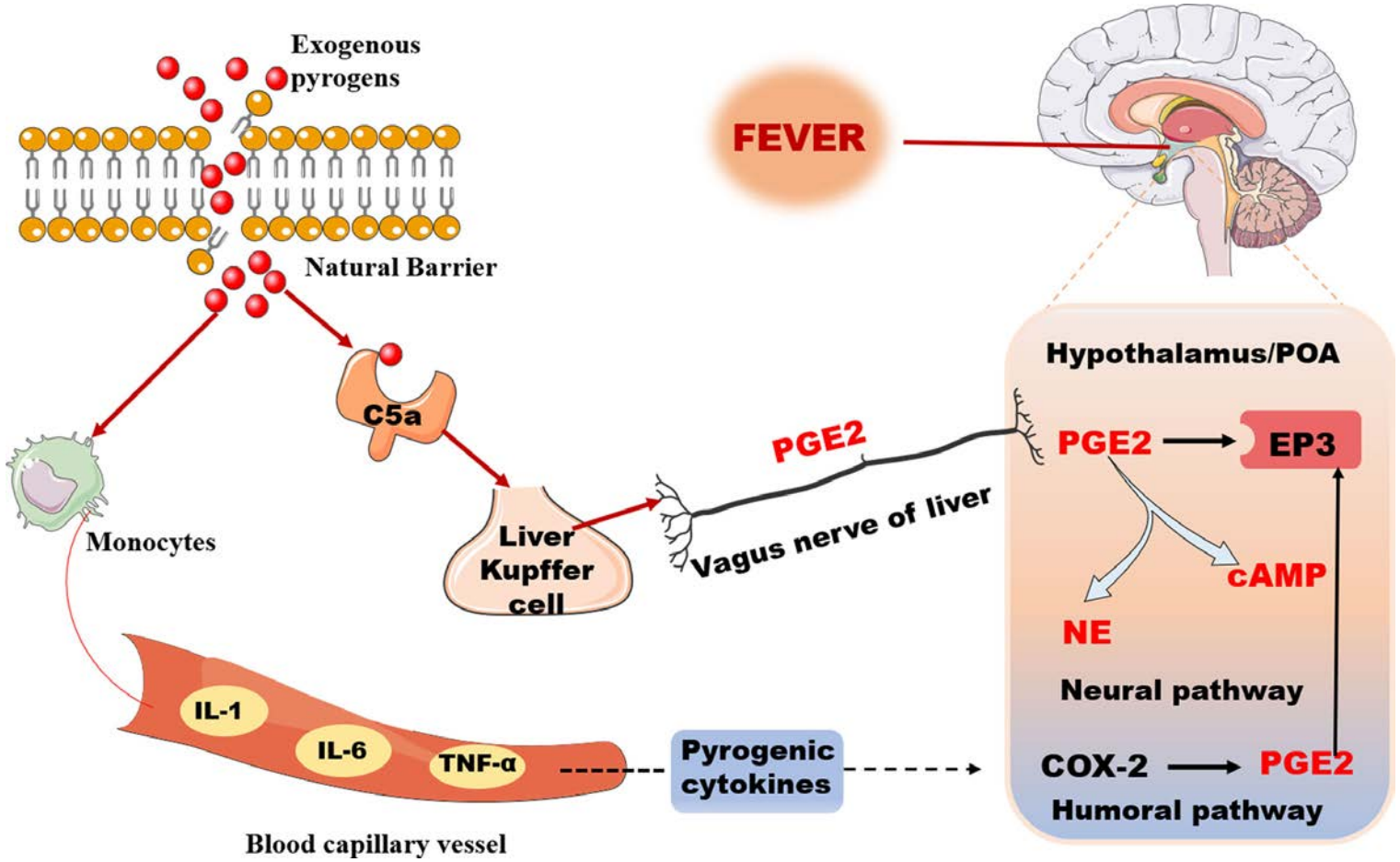
Fever Science – What is ACTUALLY Happening in there?



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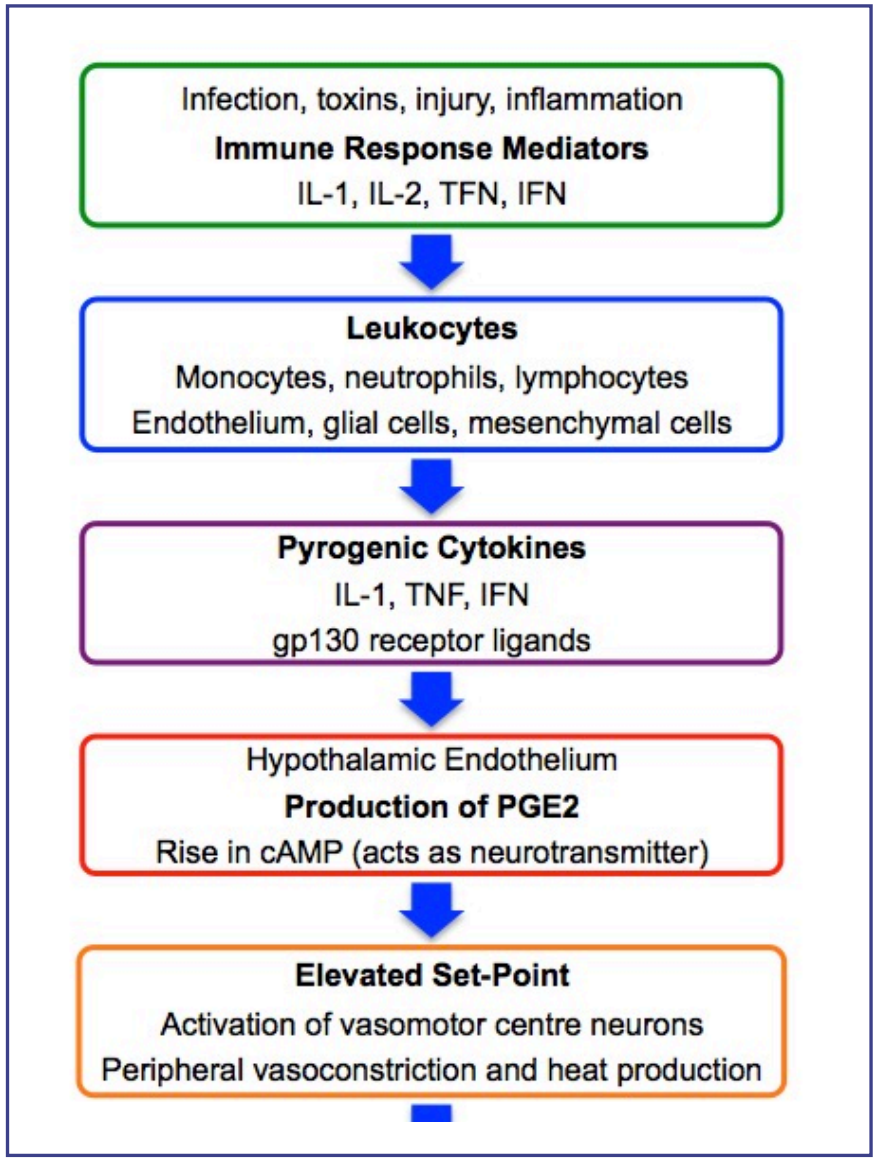
Endogenous Pyrogenic Cytokines

- IL-1
- IL-2
- IL-6
- TNF
- PGE2



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IL-1

- Interleukins = cytokines that act between leukocytes
- Exogenous pyrogens induce macrophages and other innate cells to produce IL-1 to signal fever
- IL-1 = first endogenous pyrogen discovered (Gery & Waksman 1972)
- Beeson named it Endogenous Pyrogen (EP) in 1942
- IL-1 receptors in brain, mostly hypothalamus
- IL-1 transmitted to pre-optic area of the hypothalamus (POAH) to produce PGE2, raising the **SET-POINT**

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IL-1

- Activates T and B Lymphocytes
- Induces Inflammatory response (COX 1 & 2, PGE2)
- Induces acute phase proteins (CRP, ferritin)
- Suppresses appetite
- Promotes sleep and somnolence
- Pituitary-adrenal axis stimulation
- Muscle proteolysis (breakdown)

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IL-2

Released by activated T Lymphocytes in response to exogenous pyrogen (bacteria)

Crucial effect on growth and function of T and B cells as well as Natural Killer cells

Stimulates release of IL-1, TNF, INF, and COX-2 – the big players in fever

Anti-Tumor cytotoxicity (melanoma, RCC, AML)

Induces proliferation and activation of Cytotoxic T Lymphocytes (CTLs)

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IL-6

- Secreted by macrophages and T Lymphocytes
- Stimulates both B cells and T cells to fight infection
- Acts on hepatocytes to produce CRP, amyloid and haptoglobin (acute phase)
- Early marker of infection
- Induces inflammation via COX 1 and 2

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TNF

- Pro-Inflammatory cytokine (COX1/2) Discovered in 1975

Like IL-1:

- Produced by innate cells (macrophages, lymphocytes, NK cells); by liver cells (Kupffer cells), and CNS cells (astrocytes and microglia)
- Acts on hypothalamus (POAH)
- Enhances host defense against infection & promotes healing
- Stimulates acute phase response (with IL-1 and IL-6)

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PGE2

- Endogenous pyrogens (EPs) act on the Pre-Optic Area of the Hypothalamus (POAH)
- EPs enter the OVLT & stimulate PGE2 production
- PGE2 diffuses into POAH and turns up the SET-POINT = fever
- Set-point goes back down when EP cytokines decrease
- Set-point also decreased by antipyretics that decrease PGE2

Endogenous Cryogens (ECs)

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- Term first coined by Kluger and D'Alecy in 1987
- Counteract effects of the EPs with anti-pyretic effects

- **Arginine Vasopressin (AVP):**
  - Produced in post. pituitary, synthesized by hypothalamic neurons (binds V_1)
  - Reduces set-point (reduces PGE2 and increases α-MSH)
  - Sodium salicylate stimulates AVP release, not just PGE2 inhibition

- **Alpha-melanocyte stimulating hormone (α-MSH)**
  - Peptide from pituitary and hypothalamus
  - 25,000 times more potent than acetaminophen in antipyresis in rabbits
  - Immunosuppressive effects (not surprising as offsets EPs)

Kluger M. Fever: Role of Pyrogens and Cryogens. Physiological Reviews. Vol 71: No1, January 1991.

What do we know about suppressing fever in animals and humans?

If fever is so important, and every animal does it, why do we suppress it?

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Desert Iguanas & NSAIDS

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Gave opportunity to seek heat via sunlamps

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Ferrets, Influenza & NSAIDS

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- Looked at the effects of suppressing fever, on the viral levels in nasal washes of ferrets, infected with recombinant influenza virus A
- Febrile response reduced by shaving ferrets or with sodium salicylate
- Significantly more virus was shed in the nasal washes of ferrets whose febrile response was suppressed
- And the viral levels decreased less rapidly than in untreated ferrets

THE JOURNAL OF INFECTIOUS DISEASES. Elevation of Nasal Viral Levels by Suppression of Fever in Ferrets Infected with Influenza Viruses of Differing Virulence R. H. Husseini, et al. 1982.

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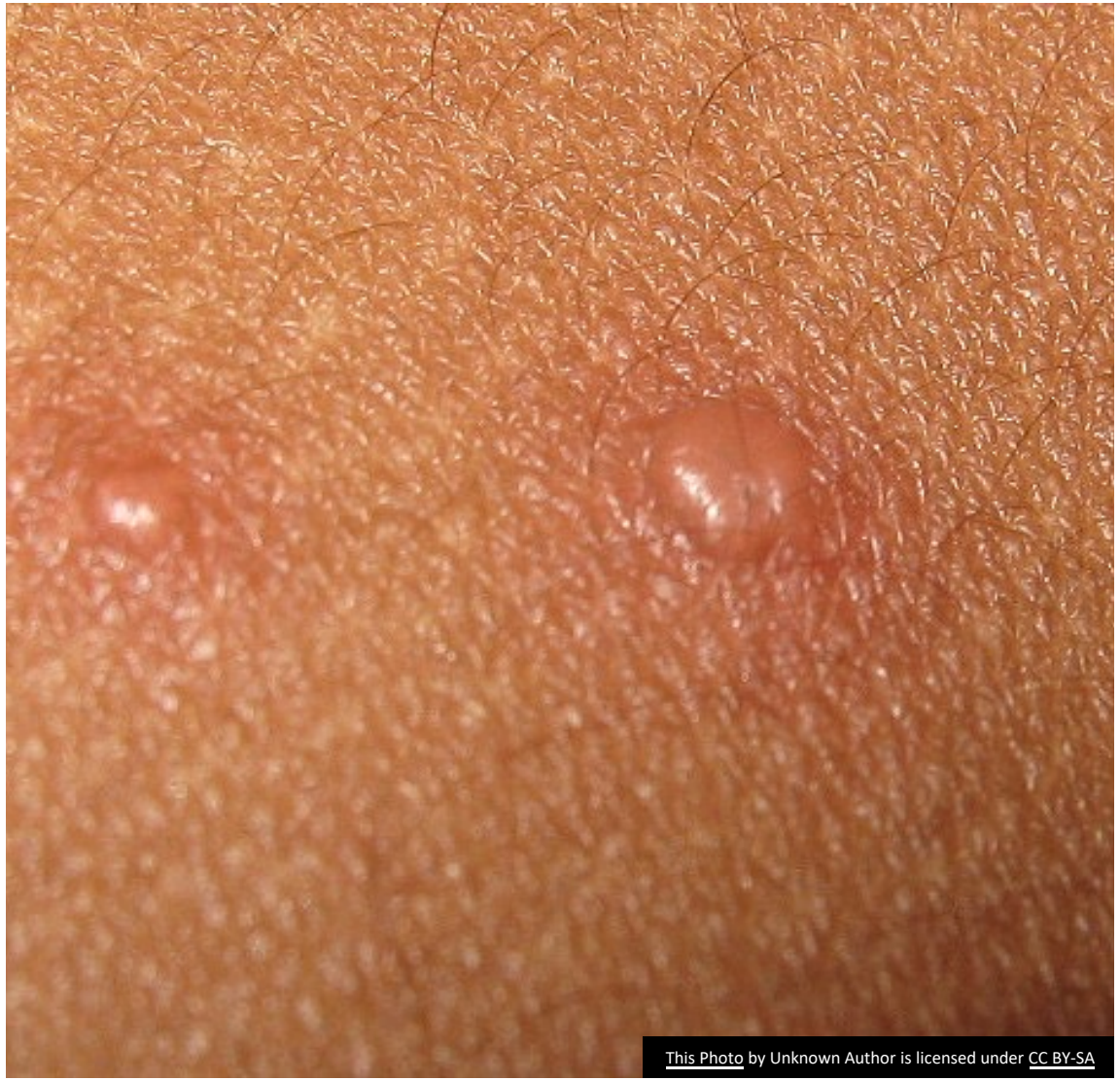
Fever suppression worsens Chicken Pox

- RCT of 72 children under 12 years of age, 31 in placebo group & 37 in the acetaminophen group (10mg/kg Q 6-hours for 4 days)
- Itching, appetite, activity & overall condition measured for 6 days
- Time to last vesicle formation, time to total scabbing, and time to heal measured until complete resolution of the rash
- Conclusion: “Acetaminophen does not alleviate symptoms in children with varicella and may prolong illness”

Dorn TF, DeAngelis C, Baumgardner RA, et al. Acetaminophen: more harm than good for chicken pox? J Pediatr 1989;114:1045–8.



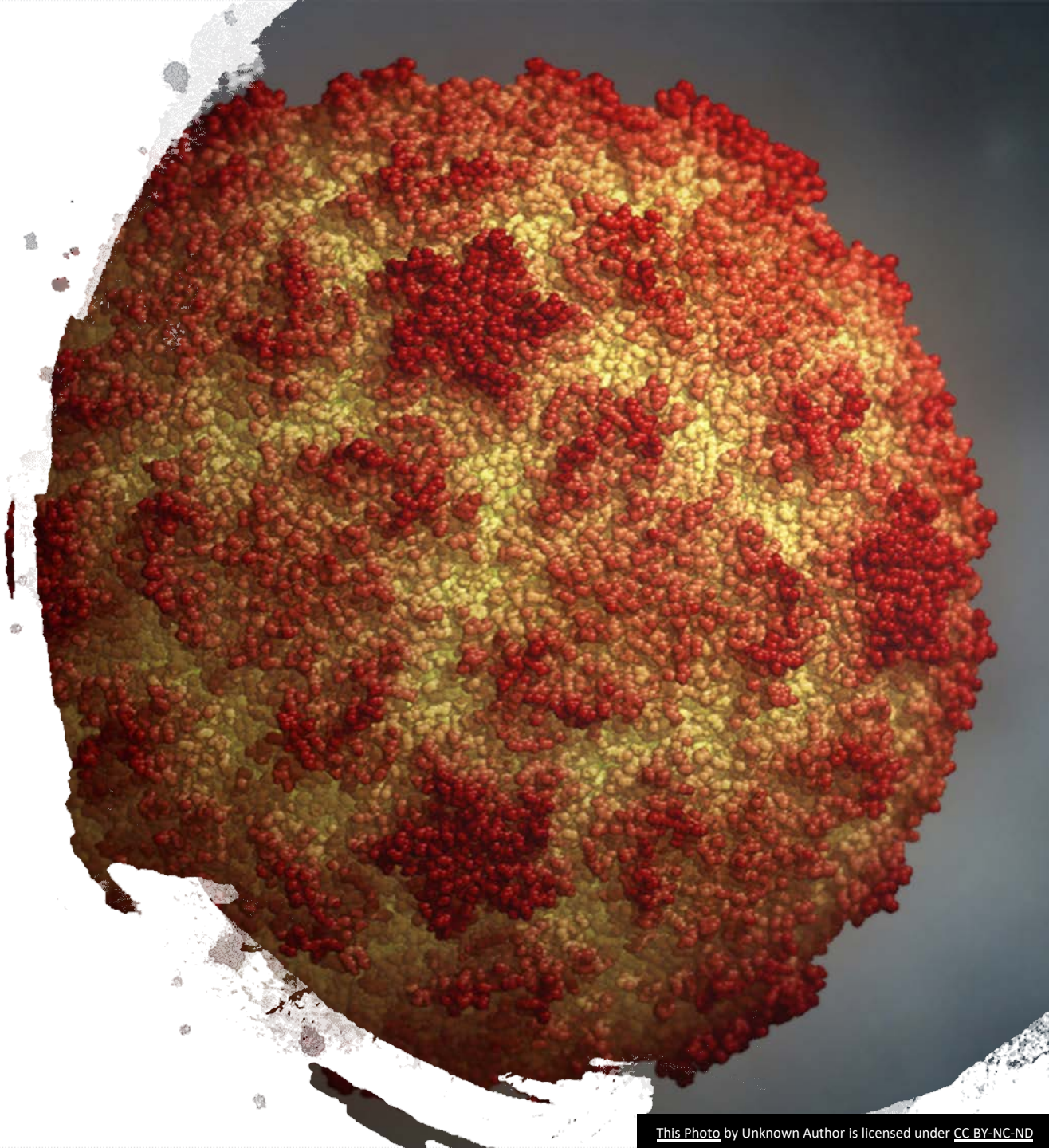
Fever Suppression worsens Rhinovirus

- In 1975 Stanley et al. reported in JAMA that adults infected with rhinovirus exhibit more nasal viral shedding when given aspirin than when given placebo

Stanley ED, Jackson GG, Panusarn C, et al. Increased viral shedding with aspirin treatment of rhinovirus infection. JAMA 1975;231:1248–51.

- In 1990 Graham et al. reported that WITH aspirin & acetaminophen, there was a longer duration of rhinovirus shedding, suppression of serum-neutralizing antibodies, and increased nasal signs & symptoms than in placebo group

Graham MH, Burrell CJ, Douglas RM, et al. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. J Infect Dis 1990; 162: 1277–82.



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2005 I.C.U. Study

- In this RCT, patients were randomized to:
  - **Aggressive Group** - Acetaminophen 650 mg every 6 hours for fever **>38.5 ℃** with addition of a cooling blanket for temperature of **>39.5 ℃**
  - **Permissive Group** - Treatment was initiated at a temperature of **>40 ℃** with acetaminophen and cooling blankets.

* The study had to be terminated at the interim analysis as there were seven deaths in the aggressive group, and only one death in the permissive group

Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. Surg Infect (Larchmt). 2005;6:369-75.

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2015 NEJM Paul Young HEAT Trial

- Prospective RCT including **700 ICU patients** with fever of known or suspected infectious etiology
- Randomized to one of the following two groups until ICU discharge, resolution of fever, cessation of antimicrobials, or death:
  - Group 1 – 1 g IV acetaminophen Q 6 hours
  - Group 2 - Placebo IV Q 6
- Patients in the treatment group had slightly lower mean daily average temperature (absolute difference −0.28 ℃, P<0.001). Not clinically significant.
- No difference in main outcome = ICU-free days until day 28
- No difference in secondary outcomes, including 28 and 90-day mortality and ICU and hospital length of stay

Young P, Saxena M, Bellomo R, et al. Acetaminophen for Fever in Critically Ill Patients with Suspected Infection. N Engl J Med 2015;373:2215-24.

2019 Paul Young REACTOR Trial

- RCT with **184 adults** without **acute brain pathologies** with a fever in previous 12 hours, & expected to be ventilated beyond the calendar day after recruitment, to one of two groups:
  - Systematic prevention & treatment of fever
  - Usual care (leave fever alone)
- Primary outcome was mean body temperature in the ICU within 7 days of randomisation
- Secondary outcomes included in-hospital mortality, ICU-free days and survival time censored at hospital discharge
- 23 of 89 patients assigned to active management (25.8%) and 23 of 89 patients assigned to usual management (25.8%) died in hospital
- No statistically significant differences between groups in ICU-free days or survival to day 90

Randomised evaluation of active control of temperature versus ordinary temperature management (REACTOR) trial Paul J. Young, Michael J. Bailey, et al. Intensive Care Med (2019) 45:1382–1391

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When Fever SHOULD be managed?

Absolute Indications:

- Traumatic brain injury

Relative Indications:

- Very weak, frail, and elderly patients
- Severe cardiovascular disease
- Severe pulmonary disease
- Cachexia
- Children between ages 3 months and 5 years (antipyretics not sown to protect against recurrence of febrile seizures)

A Little Walk Down Memory Lane on FEVER THERAPY

- “Afebrile Diathesis” observations
- Dr. Wilhelm Busch (Germany)
- Dr. William B. Coley (USA)
- Dr. Klyuyeva (Russia)
- Dr. Julius Wagner Juaregg (Austria)

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Give me the power to produce fever, and I will cure any disease"

Parmenides
(c. 515-450 B.C.)

Thomas Sydenham (1966)
Father of English Medicine
Author of *Observationes Medicae*, the standard textbook of medicine for two centuries

“Fever is nature’s engine which she brings into the field to remove her enemy”

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Afebrile Diathesis

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In 1854, JZ Laurence in “The Diagnosis of Surgical Cancer” noted cancer patients had “a remarkable disease-free history.”[1]

In 1910, Schmidt termed this “afebrile diathesis” correlating a lack of fevers to cancer risk in his study of 241 cancer patients.[2]

Several doctors published similar observations & case control studies that those suffering less infections appeared to have higher rates of cancer.[3-5]

Anecdotally, I have also observed the same remarkable fever-free history in the thousands of cancer patients I have asked/documented

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Afebrile Diathesis (References)

Laurence JZ. *The Diagnosis of Surgical Cancer. (The Liston Prize Essay for 1854.)*. London: John Churchil; 1855.

Schmidt K. Krebs und Infektionskrankheiten. *Med Klin Wschr*. 1910;43:1690-1693.

Engel P. Uber den Infektionsindex der Krebskranken. *Wien Klin Wochenschr*. 1934;47:1118–1119.

Engel P. Über den Einfluss des Alters auf den. Infektionsindex der Krebskranken. *Wien Klin Wochenschr*. 1935;48:112.

Newhouse ML, Pearson RM, Fullerton JM, Boesen EA, Shannon HS. A case control study of carcinoma of the ovary. *Br J Prev Soc Med*. 1977;31(3):148-153.

Rønne T. Measles virus infection without rash in childhood is related to disease in adult life. *Lancet (London, England)*. 1985;1(8419):1-5.

Fever Therapy

Professor Wilhelm Busch (1868)

Observed and reported a case of head and neck sarcoma that resolved after erysipelas infection

Erysipelas caused by *Streptococcus pyogenes*

He treated a 19-year-old girl with a large sarcoma of the neck, using soiled dressings from the adjacent patient with a severe erysipelas infection

She experienced a dramatic reduction to the size and density of this tumour

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Fever Therapy: William B. Coley, MD (New York)

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- **1891** Coley treated a large unresectable neck sarcoma with erysipelas bacteria from Robert Koch's German lab
- Mr. Zola developed a fever over 40℃ with pain and vomiting
- At the end of two weeks the neck tumor was not visible
- He was in excellent health when Dr. Coley saw him 4 years later
- William Coley published his early experiments "The treatment of malignant tumors by repeated inoculations of erysipelas: a report of ten original cases. American Journal of Medical Science. **1893**.

William B. Coley, MD

Father of Immuno-therapy

Over 40+ years Coley administered several combinations of bacteria including *Streptococcus pyogenes & Serratia merescens*

As head of the Bone Tumor Service at Memorial Hospital, Coley injected >1000 cancer patients

His products became known as **Coley's Toxins**

Many doctors reported excellent results in several cancers, especially in bone and soft-tissue sarcomas

Modern immunology has shown that Coley's principles were correct and that enhancing the immune system is effective for many cancers

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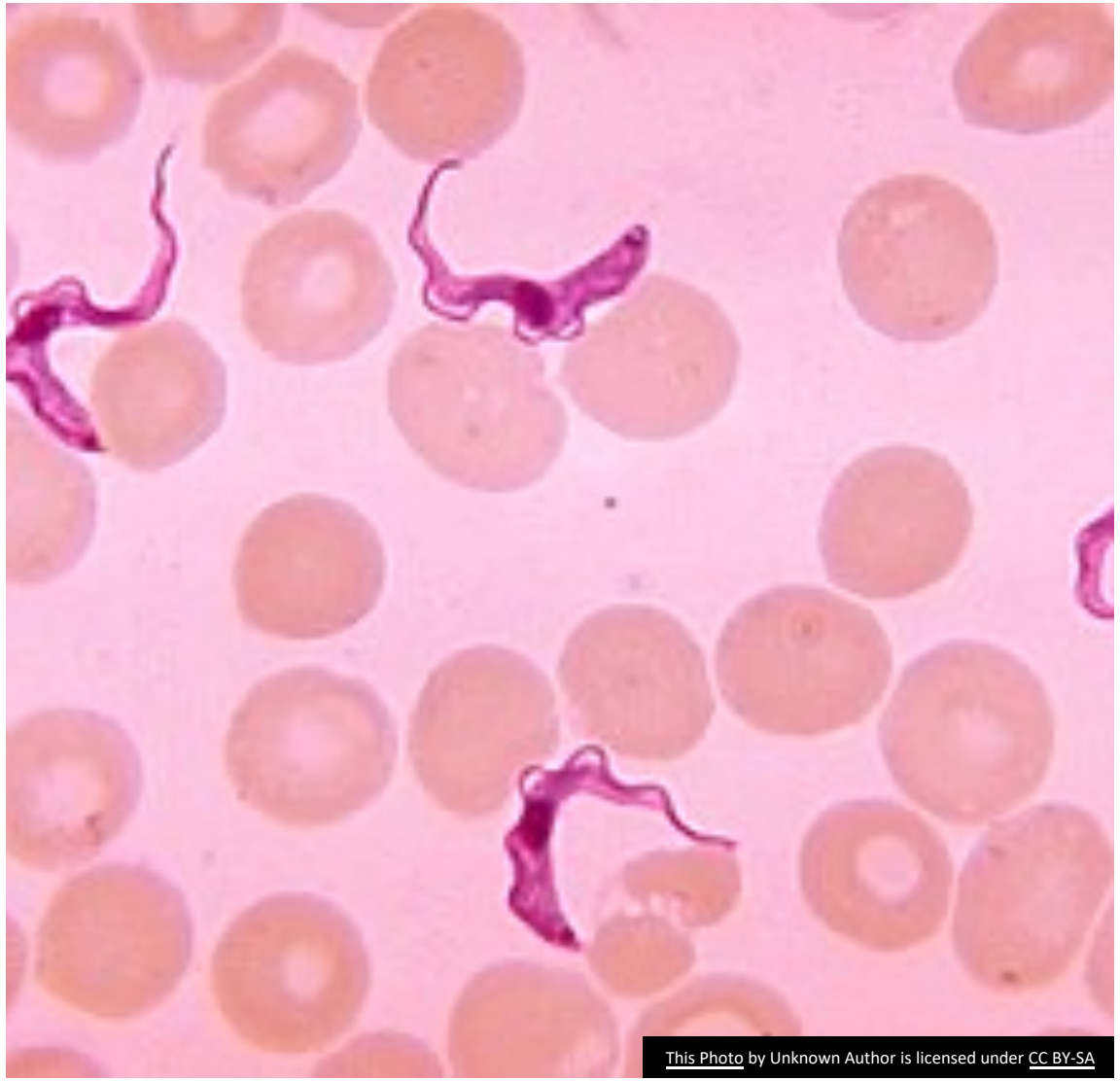
Dr. Klyuyeva (Russia)

1946 to 1953 Klyuyeva and colleagues treated cancer patients with *Trypanosoma*, the parasite of Chaga's Disease

Like *Streptococcus*, this parasite produces pattern recognition receptor ligands (PRRL), which act as antigens, which activate DCs

Concept inspired by the observation that the majority of cancer patients in Brazil were Machado-reaction-negative, where Chaga's was endemic (10-20% of population had + Machado) at that time

Klyuyeva published a book of 32 cases of complete remissions, including pictures & labs, with 11 of those patients observed > 5 years



Julius Wagner-Juaregg

(1927 Nobel Prize in Medicine or Physiology)

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In **1887** Juaregg proposed malarial fevers as treatment for general paralysis/neurosyphilis

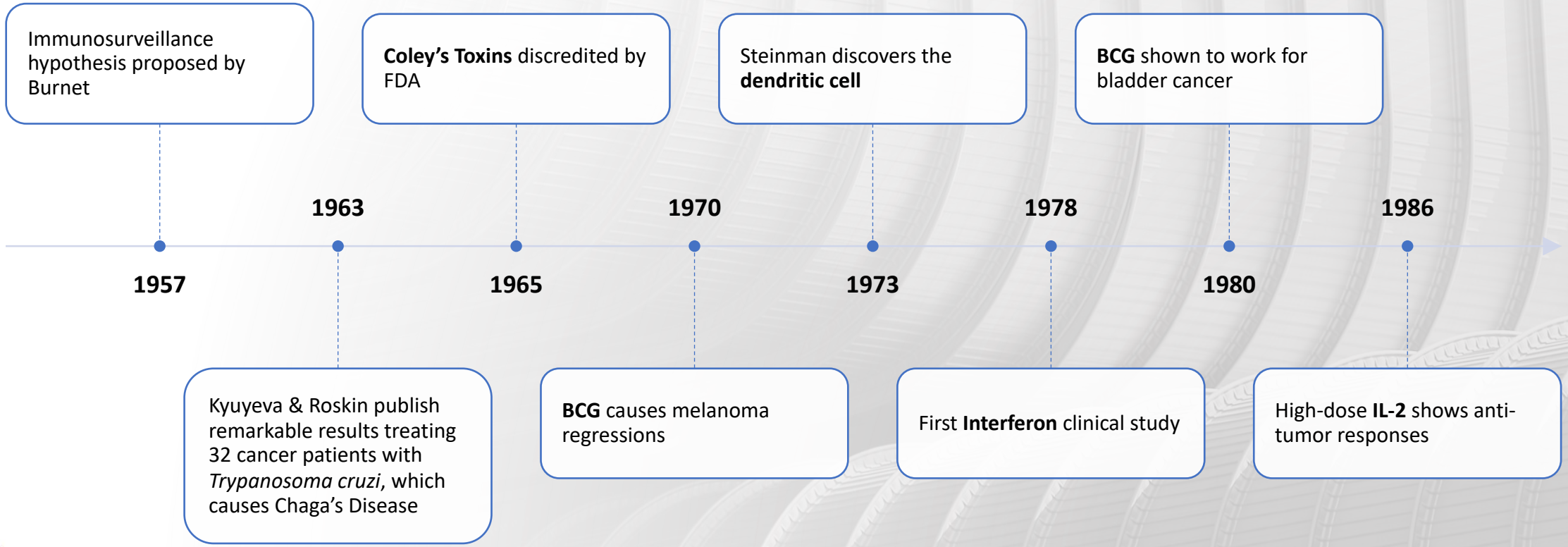
There was no antibiotic for syphilis at the time, but quinine was already available for malaria

Proof of concept was that neurosyphilis was very rare in India and China, where malaria was endemic

In **1917** he treated 9 patients with neurosyphilis paralysis, and completely cured 3 of the 9 with malaria

Subsequently, he inoculated thousands of patients over decades, curing over 30%, earning him the **1927** Nobel Prize

Let’s Fast Forward to Today



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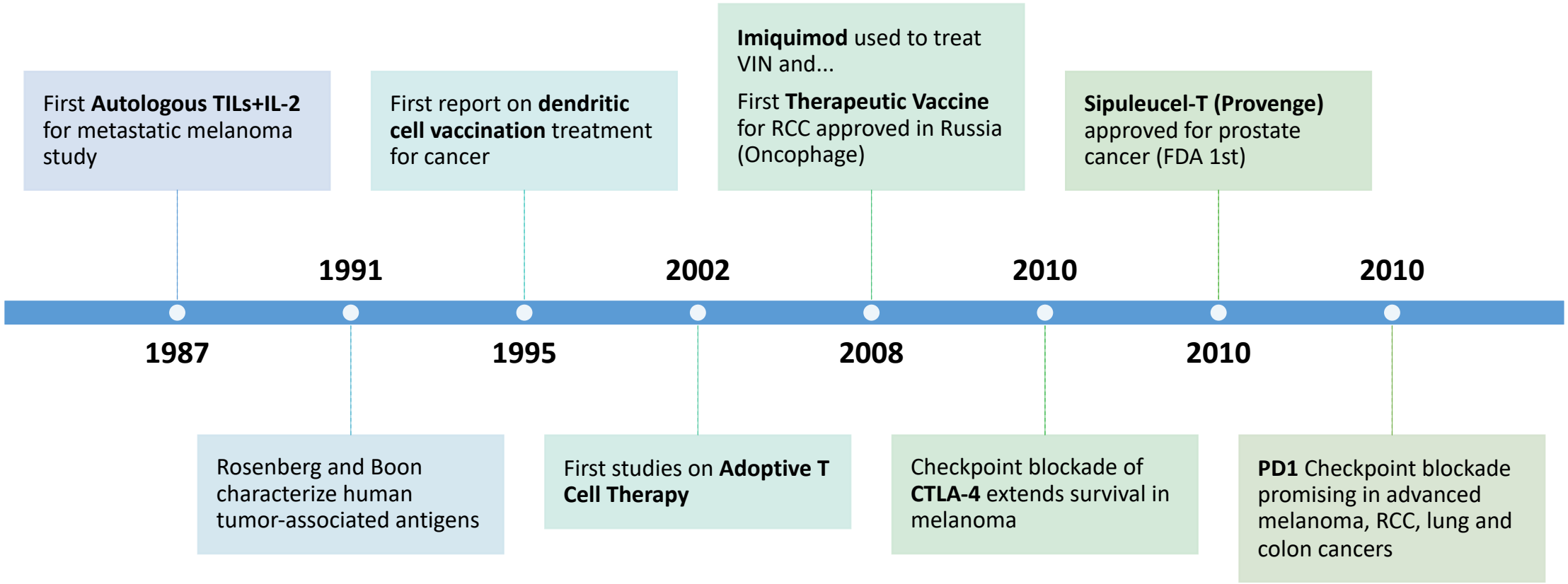
Immunotherapy Timeline Continued



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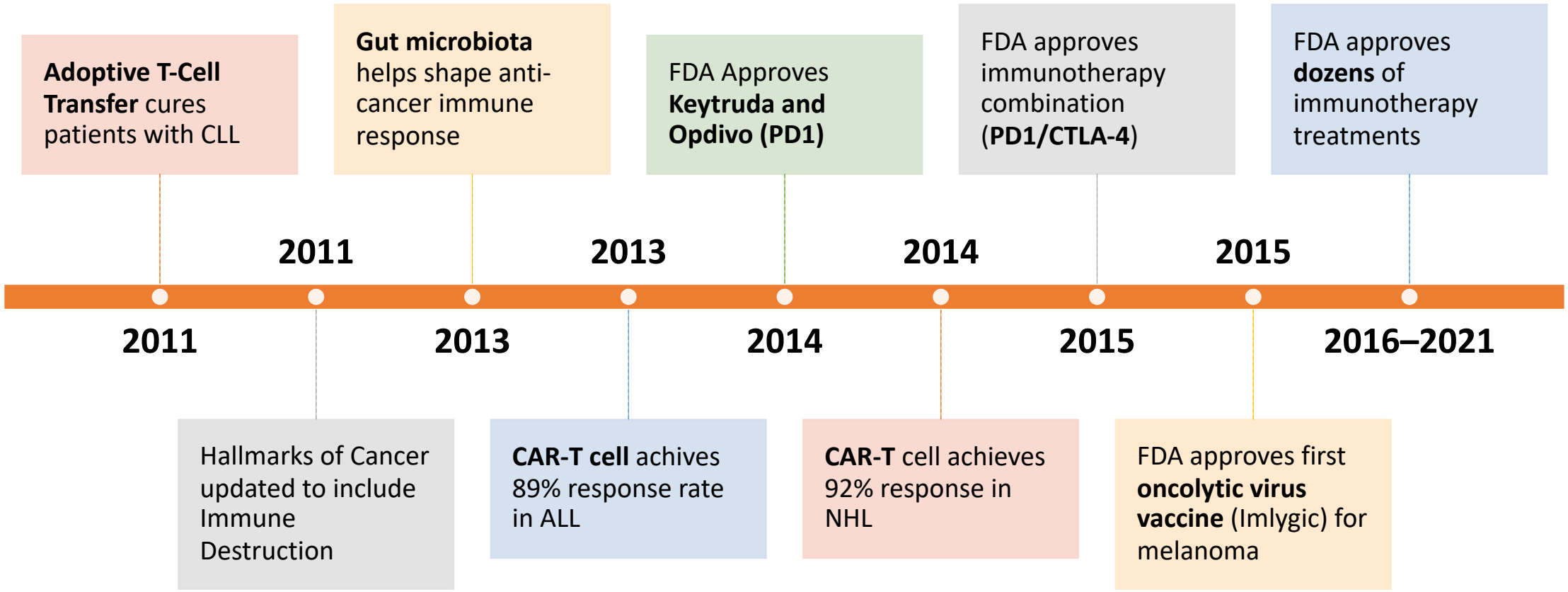
Immunotherapy Timeline Continued



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Immunotherapy Today:

4 Major Classes

Immune Checkpoint Inhibitors

- PD1/PD-L1
- CTLA-4

Adoptive Cell Transfer

- TIL's
- CAR-T

Therapeutic Vaccines Strategies

- Autologous
- Non-Autologous

Non-Specific Immunomodulators/Stimulation

- Interferons/Interleukins
- BCG
- Biological Response Modifiers (thalidomide's)

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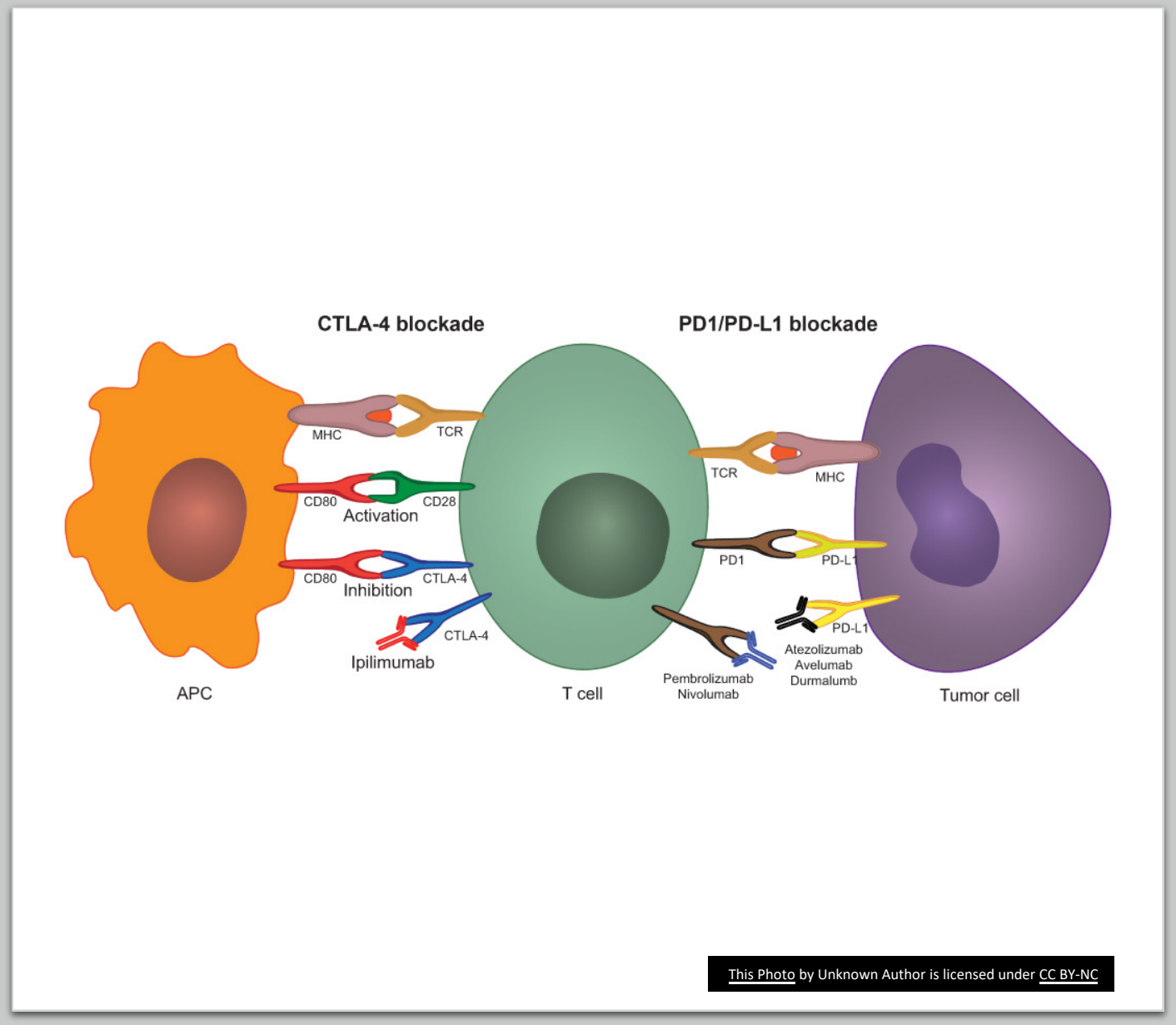
Immune Checkpoint Inhibitors

- **Early Co-Inhibitory signals**
  - **CTLA-4** (on T Cell) with **B7** (Tumor cell/APC)
  - More important during INDUCTION phase of T cell response
- **Late Co-Inhibitory Signals**
  - **PD1** (on T Cell) with **PD-L1** (Tumor cell/APC)
  - More prominent role during EFFECTOR phase of T cell response

CONS:

- Not patient-specific
- Expensive per patient
- Lack specificity in immune activation often leads to severe autoimmune SE's



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Immune Checkpoint Inhibitors

Cancer types	Blocking agents	Clinical response rate
Melanoma	Nivolumab	12.8% in treatment-refractory metastatic melanoma, 28% in advanced melanoma, 40% in melanoma treated in combination with ipilimumab, 20% in nivolumab followed by iplimumab, 40% in previously untreated melanoma without BRAF mutation, 57.6% (nivolumab plus iplimumab) versus 19% (ipilimumab) versus 43.7% (nivolumab) in untreated stage III or IV melanoma
	Pembrolizumab	38% in comparison to chemotherapy (14%), 26% in ipilimumab-refractory advanced melanoma, 33% in comparison to ipilimumab (11.9%) in advanced melanoma
	Atezolizumab	21% objective response rate
	MDX-1105	17.3% objective response rate
NSCLC	Nivolumab	12.8% in treatment-refractory metastatic NSCLC, 18% in advanced NSCLC, 14.5% in refractory NSCLC, 17% in previously treated NSCLC, 20% in advanced squamous cell NSCLC, higher overall survival (12.2 months) versus docetaxel treatment (6 months)
	Pembrolizumab	63 versus 0% in stage IV NSCLC patients with high and low non-synonymous mutation burden, 19.4% in advanced NSCLC of unselected population, 45.2% objective response rate in PD-L1$^+$ population
	Durvalumab	14% objective response rate in unselected population and 23% in PD-L1$^+$ population
	Atezolizumab	15% objective response rate in unselected population and 38% in PD-L1$^+$ population
	MDX-1105	10.2% in NSCLC
Renal cell carcinoma	Nivolumab	Higher overall survival (25 months) and better objective response rate (25%) in comparison to everolimus treatment (19.6 months and 5% ORR)
	Atezolizumab	21% overall response rate
	MDX-1105	11.7% response rate
Breast cancer	Atezolizumab	19% objective response rate
	Pembrolizumab	18.5% response rate
Small cell lung cancer	Nivolumab	18% objective response rate in monotherapy and 17% objective response rate in combination
	Pembrolizumab	35% response rate
	Atezolizumab	21% objective response rate
Head and neck	Durvalumab	12% objective response rate
	Pembrolizumab	24.8% objective response rate observed in both HPV$^+$ and HPV$^-$ patients
	Atezolimumb	19% objective response rate
Hepatocellular carcinoma	Nivolumab	19% objective response rate
Gastric cancer	Nivolumab	31% response rate
	Atezolizumab	21% overall response rate
Ovarian cancer	Nivolumab	15% response rate, responses lasted up to 17 months
	Avelumab	14.7% objective response rate
	Pembrolizumab	11.5% response rate
	Atezolizumab	21% overall response rate
	MDX-1105	5.9% response rate
Bladder cancer	Atezolizumab	26% objective response rate in unselected population and 43% in PD-L1$^+$ population
	Pembrolizumab	25% objective response rate in unselected population and 38% in PD-L1$^+$ population
Mismatch repair-deficient carcinoma (colorectal and other)	Pembrolizumab	40% objective response rate in repair-deficient CRC, 0% in repair-sufficient CRC, 71% in mismatch repair-deficient non-colorectal carcinomas
Merkel cell carcinoma	Pembrolizumab	71% objective response rate
Hodgkin's lymphoma	Nivolumab	87% objective response in relapsed or refractory Hodgkin's lymphoma
	Pembrolizumab	66% overall response rate

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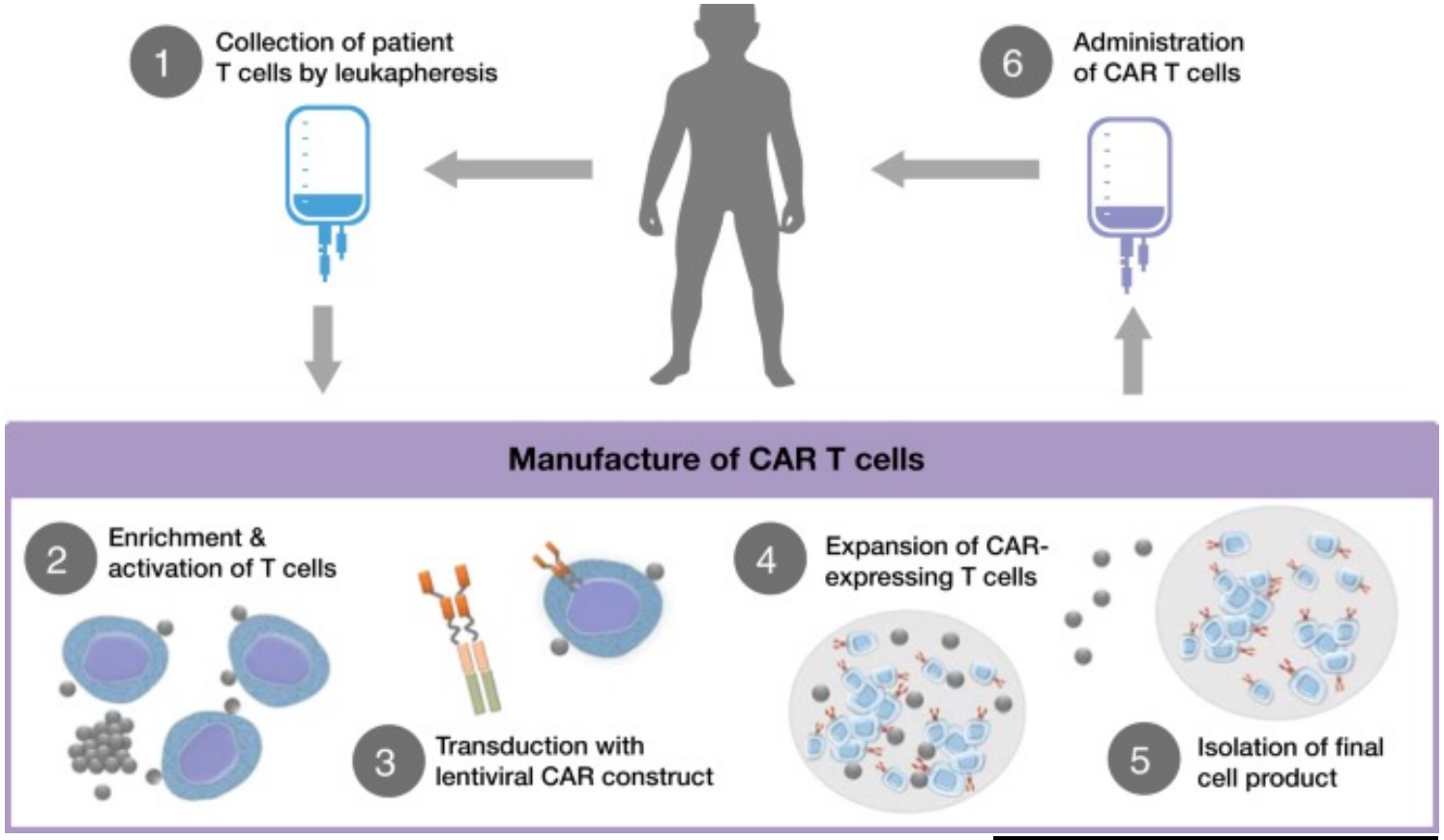
Adoptive Cell Transfer: CAR T-Cell Therapy

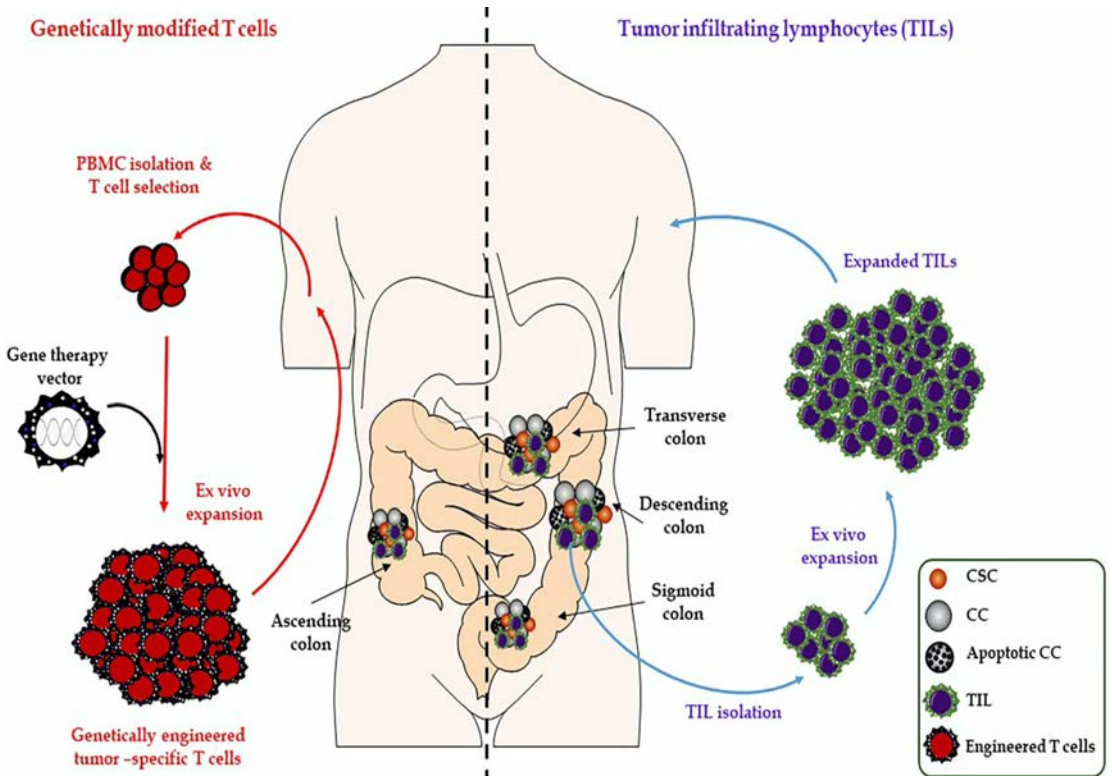


- **C**himeric **A**ntigen **R**eceptor **T Cells** (CAR T Cells)
- Peripheral blood T cells genetically engineered to express tumor-antigen-specific T cells, then administered to patient

CONS:

- Very expensive per patient cost ($400K USD)
- Long and slow process on a patient-by-patient basis

Adoptive Cell Transfer: Tumor-Infiltrating Lymphocytes (TIL's)



- Lymphocytes = 20-40% of WBCs
- In circulation and concentrated in lymphatic system
- Determine specificity of immune response to bugs/cancer cells
- T lymphocytes from the tumor cultured and expanded ex vivo in the presence of IL-2
- When there are enough T lymphocytes, they are reinfused into the patient

CON:

- Difficult to obtain enough T cells

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Non-Specific Immune Stimulation: **IFNα & IL-2**

First study on IFNα in melanoma published in 1985

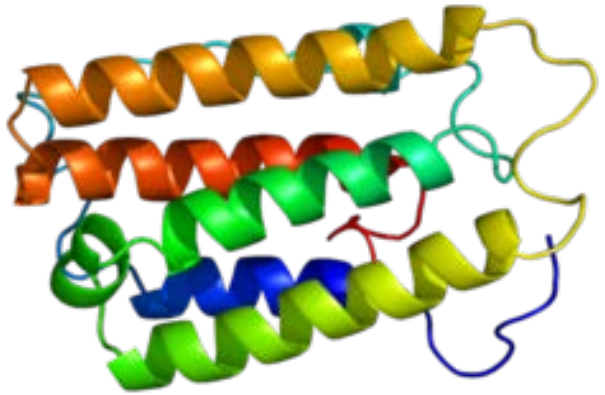
- Approved for melanoma and RCC with complete responses

First study on IL-2 published in 1983

- Durable complete remissions in melanoma possible

CONS for both:

- Require prolonged use
- Non-specific immune effects (not targeted or tumor-specific)
- Have some significant SE's (hematologic, hepatic, etc.)



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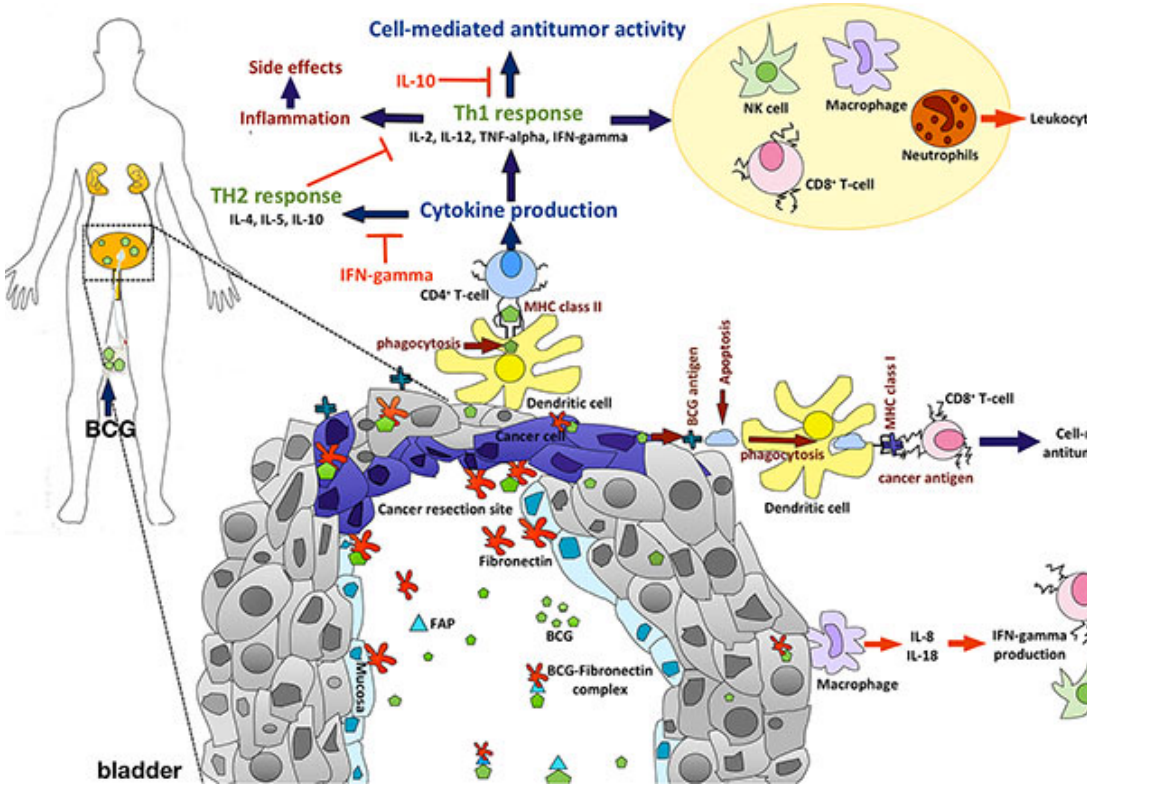
Non-Specific Immune Stimulation: BCG

- Bacillus- of Calmette & Guerin (BCG) = live bacterial culture
- Strain of *Mycobacterium bovis* = *Mycobacterium tuberculosis* vaccine
- Creates a complete immune response in the bladder, as with Coley's toxins, including IL-2, IFNα, TNF, macrophages, dendritic cells, etc.
- Closely resembles a complete "fever-like" response as with *Streptococcus*, *Trypanosoma*, and *Plasmodium*



Tumor Vaccination Strategies

Goal is to “re-educate” endogenous T cells by presenting tumor Ag’s

Tumor Ag’s are harvested from tumor or blood, synthetically produced, or encoded by plasmid DNA/virus

For all vaccines, ADJUVANTS such as TLR-agonists or GM-CSF are required to “activate” them

Tumor Ag’s are collected (tumor or peripheral blood), cultured, activated by cytokines and/or adjuvants ex-vivo, then administered to the patient

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Tumor Vaccination Strategies: Examples

- Sipuleucel-T = first autologous APC vaccine loaded with Prostatic Acid Phosphatase
- Dendritic cell vaccines (autologous DC's loaded with tumor Ag's)
- ProstVac (Poxvirus-based PSA-targeted vaccine)
- OncoVEX (attenuated HSV1 encoding human GM-CSF)

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Naturopathic Immunotherapy: FR-WBHT

- Artificial induction of a fever using IR-A heating
- Developed in Germany in the mid 1900's
- Recent Practice Guidelines published in 2018
- Many year of research in various conditions including depression, chronic pain, infections, autoimmune diseases, cancer

Fever Range Whole Body HT (FR-WBHT)

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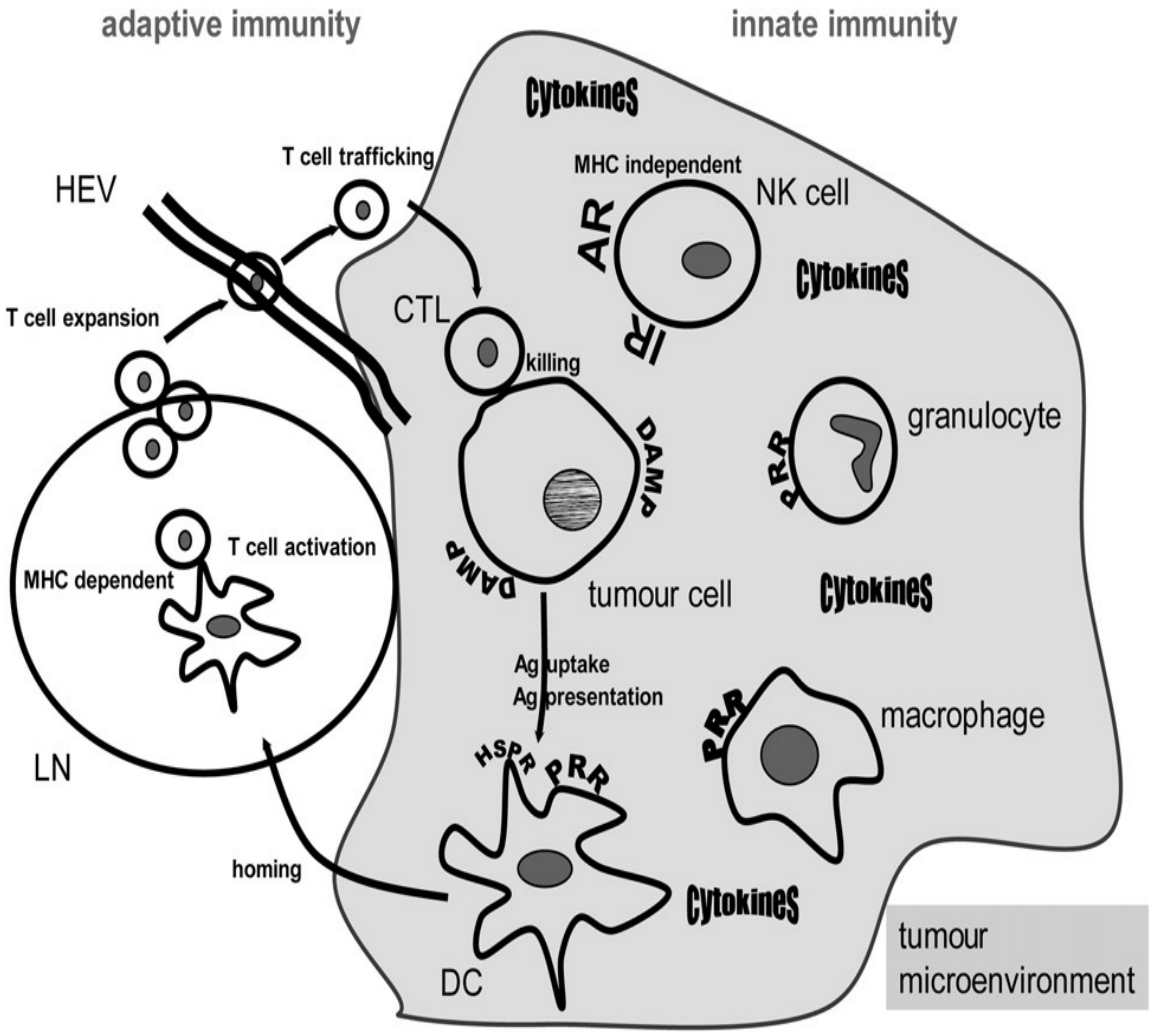
Closely resembles a fever stimulating innate and adaptive Immune Responses

Able to largely mimic a live fever, without the risk of infection worsening or worse, septicemia

Innate: Increases macrophages, NK cells, HSP's, TNF, IL-1, Il-6, neutrophils, GM-CSF

Adaptive: Increases lymphocyte trafficking, dendritic cells, Cytotoxic T Lymphocytes



Modulated Electro-Hyperthermia (mEHT)

mEHT modulates innate & adaptive immune responses

HT damaged tumor cells expose DAMP, recognized by innate cells via pattern recognition receptors (PRR)

DCs take up HSP/tumor Ag complexes via HSP receptors (HSPR), and present to T cells

HT induces maturation & migration of DCs to LNs where they activate T cells

Finally, DCs activate tumor-Ag cytotoxic T lymphocytes

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Modulated Electro-Hyperthermia (mEHT)

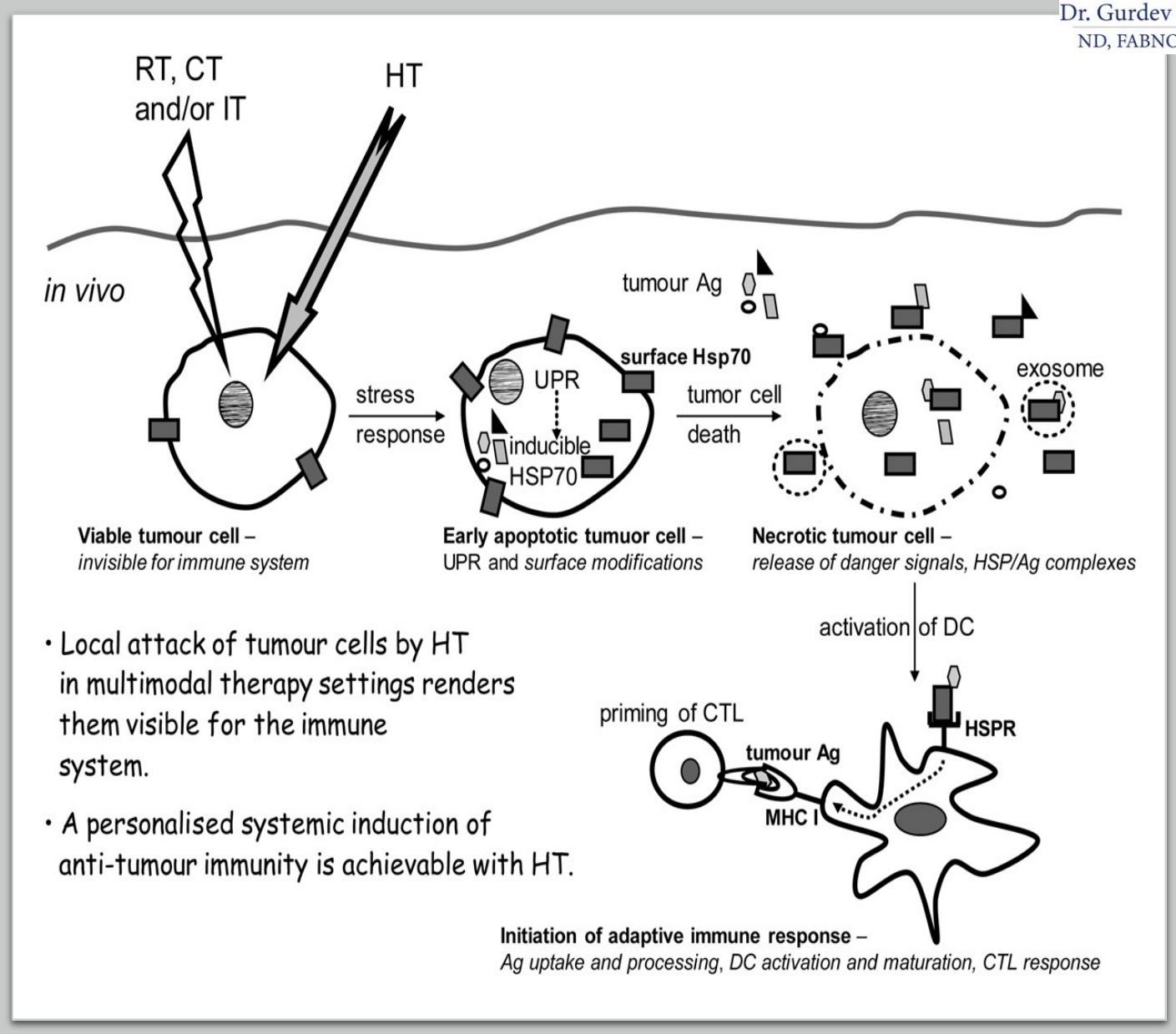
Again, the mEHT modified tumor cells are rendered immunogenic thus called an “in situ tumor vaccine therapy”.. How?

Protein aggregation & denaturation induces unfolded protein response (stress response)

HSPs act as danger signals attracting DCs

HSP/tumor Ag complexes are released activating and attracting DCs

DCs take up tumor Ag and present to and prime the cytotoxic T lymphocytes (CTLs)



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Naturopathic Immunotherapy: Microbiome

Composition of intestinal microbiome modulates response to checkpoint inhibitors in melanoma, RCC and NSCLC (Lee, KA, et al. Role of the gut microbiome for cancer patients receiving immunotherapy: Dietary and treatment implications. Eur J of Cancer. 138(2020):149-155.)

Studies showing certain probiotics make immunotherapy treatments more effective

Association between presence of certain bacteria in gut and the efficacy of immunotherapy treatments

Antibiotics can make immunotherapy less effective

Stool of patients in whom immunotherapy DID work was administered (capsules/enemas) to patients in whom immunotherapy did NOT work, and then it DID work (Baruch, E. N. et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science https://doi.org/10.1126/science.abb5920 (2020))

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Naturopathic Immunotherapy: Mistletoe Lectin Therapy

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- Dr. Ita Wegman first prepared/administered injection >100 years ago
- Active ingredients = lectins, viscotoxins, and polysaccharides
- Increases B cells, T cells, GM-CSF, IL-1, IL-6, TNFα, NK cells, macrophages, IFN, granulocytes, etc.
- Perhaps most studied natural immunotherapy with hundreds of published human studies
- Stimulates thermoregulation - raises body temperature & can stimulate fever

Naturopathic Immunotherapy: I.V. Vitamin C

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Extensive role on immune systems's lymphocytes (T cells + NK cells)

Enhances chemotaxis and phagocytosis of neutrophils

Promotes T cell development and maturation

Promotes Th1 differentiation at expense of Th2 polarization

Shown to decrease inflammation through suppression of cox-2and nuclear factor κB (reduces hs-CRP)

Gwendolyn N, et al. Influence of Vitamin C on Lymphocytes: An Overview. Antioxidants. 2018, 7, 41; doi:10.3390/antiox7030041.

Naturopathic Immunotherapy: Medicinal Mushrooms

- **Coriolus versicolor (Turkey Tail)**
- Increases TNF, IFN, IL-2
- **Ganoderma lucidum (Reishi)**
- Increases IL-1, IL-2, IL-6, IFN, TNF, NK activity
- **Cordyceps sinensis**
- Increases IL-1, IL-2
- **Agaricus bisporis (White button)**
- Increases IFN, IL-6
- **Grifola frundosa (Maitake)**
- Increases IFN, IL-10, TNF, G-CSF

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Guggenheim AG, et al. Immune Modulation from five major mushrooms: Application to Integrative Oncology. Integrative Medicine. Vol 13. No 1. February 2014.

Naturopathic Immunotherapy: Botanical Medicines - Widely Used

Microtubule Inhibitors = naturally occurring alkaloids

- Vinca alkaloids - Madagascar periwinkle (*Canthanthus roseus*)
- Taxols = Paclitaxel (Pacific) Docetaxel (European) yew trees (*Taxus spp*.)
- Maytansine = what Herceptin is conjugated with in Kadcyla
  - Maytansine derived from bark of African shrub *Maytenus ovatus (Spike thorn)*

Topoisomerase 1- and 2- Inhibitors

- TI-1 = Camptothecins (*Camptotheca,* Happy tree) – irinotecan topotecan
- TI-2 = Podophyllotoxins (Podophyllum, May apple) – etoposide teniposide

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Naturopathic Immunotherapy: Botanical Medicines -Up and Coming

DNA Methylation Inhibitors

- EGCG = catechins from *Camellia senensis* (green tea)

Histone Deacetylase (HDAC) Inhibitors

- Pomiferin = isoflavone from *Maclura pomifera* (Osage Orange – China)
- Sulforaphane = isothiocyanate from *Brassica oleracea* (Broccoli & its sprouts)

ROS Inducers (DNA damaging/pro-oxidants)

- EGCG
- Thymoquinone = volatile oil constituent in *Nigella sativa* = black seed (Middle East)

Mitotic disrupters (Cyclin Dependent Kinase (CDK) Inhibitors

- Flavopiridol = flavonoid from *Dysoxylum binectariferum* = Mahogany (India)
- Thymoquinone

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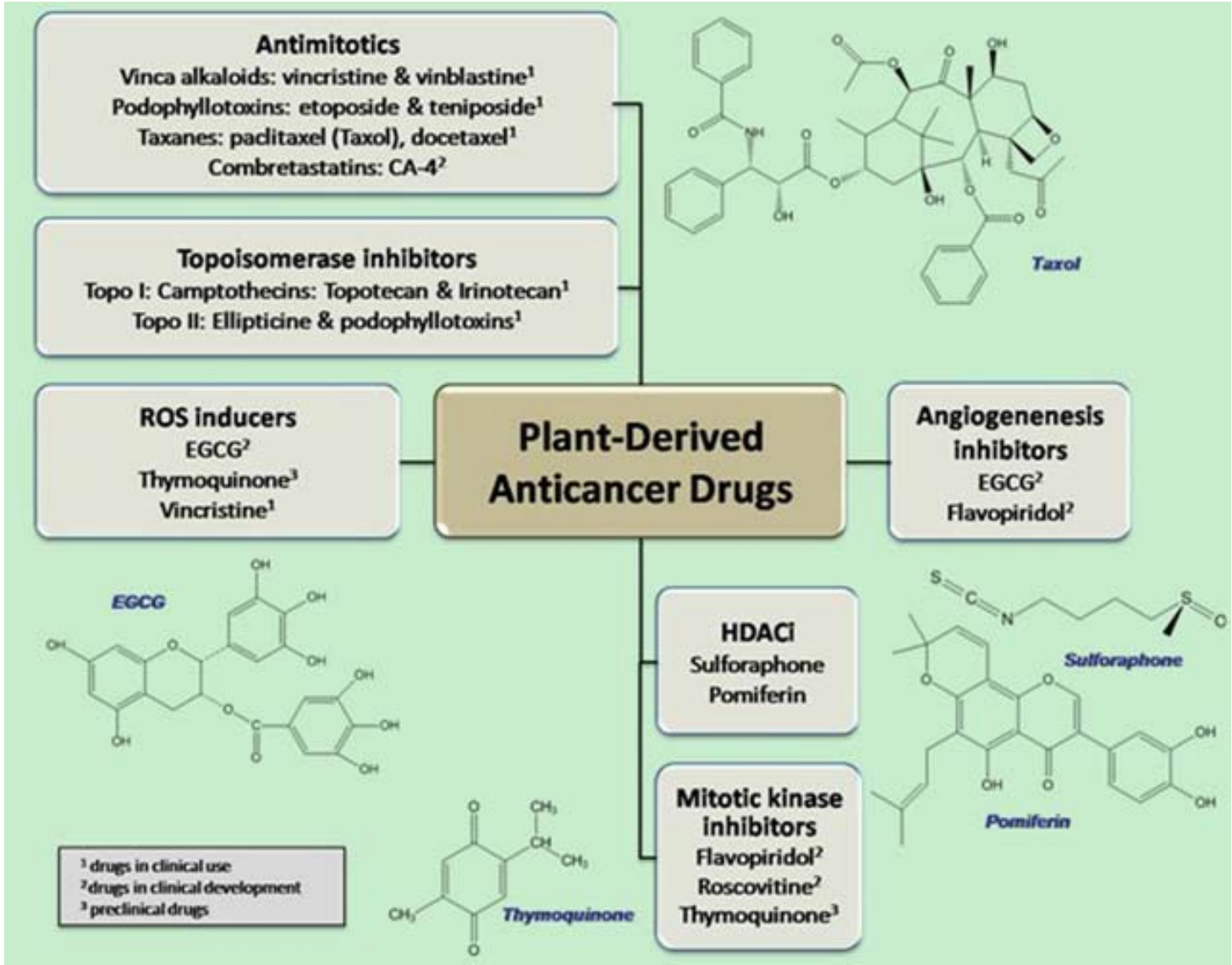
Naturopathic Immunotherapy: Botanical Medicines – Up and Coming

Amin A, et el. Overview of major classes of plant-derived anticancer drugs. Int J Biomed Sci. Vol 5(1). March 2009.



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HOT OF THE PRESS:

SARS-CoV-2-induced Remission in Hodgkin lymphoma

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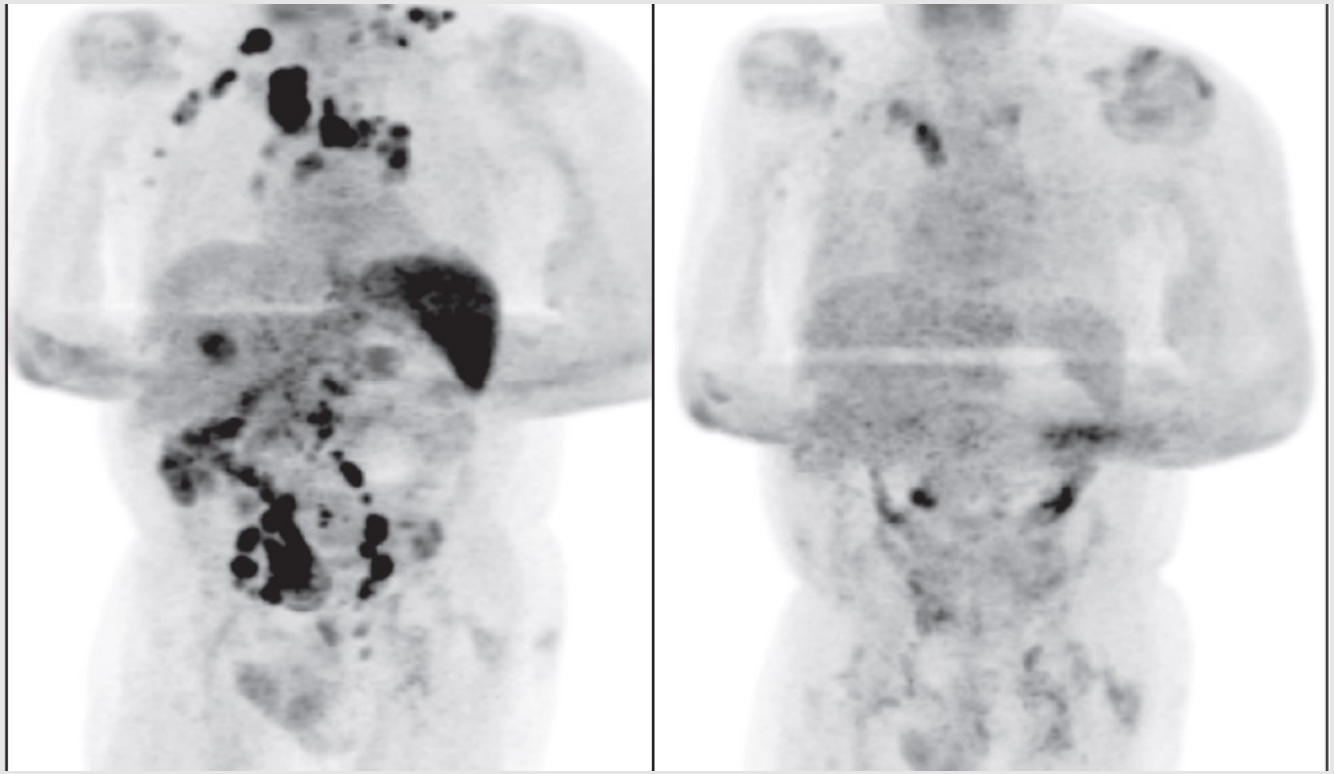

- 61-year-old man with widely disseminated, Stage IIIs EBV+ classical Hodgkin Lymphoma
- PET scan on left from time of diagnosis
- Shortly after diagnosis, admitted to ER with breathlessness and wheeze. Diagnosed with SARS-CoV-2 pneumonia, discharged after 11 days
- 4-months later, with no treatment, there was resolution of the Hodgkin Lymphoma, resolved lymphadenopathy (PET Scan on right) and EBV viral PCR fell 413 copies/ml

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My Immunotherapy Approach Today:

An evidence-informed approach

- Incorporate appropriate dietary strategies to improve immune function
- Incorporate appropriate lifestyle & mind-body strategies to improve immune function
- Incorporate hyperthermia methods for local & systemic immunity
- Incorporate mistletoe lectins & other botanical medicines
- Incorporate I.V. ascorbic acid & other pro-/anti-oxidative strategies
- Incorporate non-specific immune stimulators (IFN's, IL's)
- Incorporate tumor vaccination strategies
- ALWAYS Integrate safely & appropriately with conventional Checkpoint Inhibitors & Adoptive Cell Transfer therapies

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My Hypotheses & Fever Treatment Concept

Fever should largely be left alone. Rest. Isolate. Fever. Heal.

Allowing fevers strengthens immunity - “training exercises”

Allowing fevers will lower risk for chronic diseases & cancer

A truly comprehensive fever-inspired immunotherapy treatment would utilize multiple EP cytokines concurrently

An **EP Mixture** of lower dose IL-1, IL-2, IL-6, INF, TNF & PGE2 is safer and more effective than mono-cytokine treatment

The Parmar I.V. Fever Treatment Concept:

1. I.V. **EP Mixture** administered to reach 40-40.5°C
2. I.V. **EC** (α-MSH & AVP) administered prn to lower temperature
3. Maintain 40-40.5 °C for set time (varies for condition and patient’s health status)

Immunity Summoned:

Fever's Journey to Immunotherapy

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