IMMUNOTHERAPY

AN ESSENTIAL COMPONENT OF 21ST CENTURY CANCER THERAPY

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TALK OUTLINE

- What Is Spurring This Massive Immunotherapy Wave?
- The New Concepts in Immunotherapy and Identifying Druggable Targets
- Immunotherapy: Hype vs. Reality
- The Market Drives Accelerated Growth for Immunotherapy
- Reductionism vs. Holism/Complexity Theories
- The Seven Key Principles of Cancer Therapy
- Take Home Messages


WHAT IS SPURRING THIS MASSIVE ...
IMMUNOTHERAPY WAVE?

CONVENTIONAL THERAPIES ARE FALLING SHORT

"The standard way to treat most forms of cancer, when it comes to chemotherapy, is to hit it as hard as possible. That makes sense, and it's a natural human impulse, too: here's something that is in the process of killing the patient, so why wouldn't you go all out? But in recent years, data on what's going on inside tumor cell populations has called this approach into some doubt."

- Derek Lowe, Ph.D.

Science Translational Medicine

February 26, 2016

IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*. All content is Derek's own, and he does not in any way speak for his employer.

Derek Lowe is "America's best known medicinal chemist"; earned his Ph.D. from Duke University; worked for many pharmaceutical companies since 1989.

In 2002, he became the first industry insider to start a blog.

Source: http://blogs.sciencemag.org/pipeline/about-derek-lowe

"This all means that if you charge in and try to blast the cancer out of a patient, you're going to end up only blasting some of it out – probably the easier part, in many cases. **Oncologists have realized this for a long time, naturally, but there hasn't been much that could be done about it."**

- Derek Lowe, Ph.D.

What makes cancers difficult to treat with conventional therapies?

- **Tumor heterogeneity**
- **Genetic variability from tumor formation to metastasis**
- **Diverse metabolic pathways are difficult to target**

Source: http://blogs.sciencemag.org/pipeline/about-derek-lowe

THE RISE OF TARGETED THERAPIES

Therapies that target specific cancer-related molecular receptors/antigens:

Hormone Therapies
Signal Transduction Inhibitors
Gene Expression Modulators
Apoptosis Inducers
Angiogenesis Inhibitors
Monoclonal Antibodies that Deliver Chemotherapy
Cancer Vaccines
Gene Therapy
Immunotherapies

ERA OF DOMINANCE OF CHEMOTHERAPY AND RADIATION THERAPY

1890s
First Cancer Vaccine – Coley's Toxin

Early 1900s
First Use of Radiation Therapy for Cancer

1949
Nitrogen Mustard Becomes First Approved Chemotherapy

2014
Approval of two anti PD-1 antibodies as checkpoint inhibitors for melanoma and lung cancer
(Pembrolizumab/Keytruda®, Nivolumab/Opdivo®)

2011
First Checkpoint Inhibitor (CTLA-4) Approved for Melanoma
(Ipilimumab/Yervoy®)

2015
T-VEC Approved as Oncolytic Virotherapy For Melanoma

1968
Clinical Studies of Cancer Patients with Riga Virus Started

1973
Discovery of the Dendritic Cell

1976
First Study with BCG in Bladder Cancer

1978
Discovery of Tumor Specific Monoclonal Antibodies (mAb)

1985
First Study with Adoptive T Cell Transfer

1986
First Approved Cytokine Therapy (IFN-α)

1987
Discovery of First Checkpoint Inhibitor (CTLA-4)

1991
Discovery of GcMAF

1997
First mAb Approved for Cancer Therapy
(Rituximab Rituxan®)

1998
IL-2 Cytokine Approved for Cancer

2004
Rigvir Oncolytic Virotherapy Approved in Latvia for Melanoma

2010
First Cellular Immunotherapy Approved (Sipuleucel-T/ Provenge) for Prostate Cancer

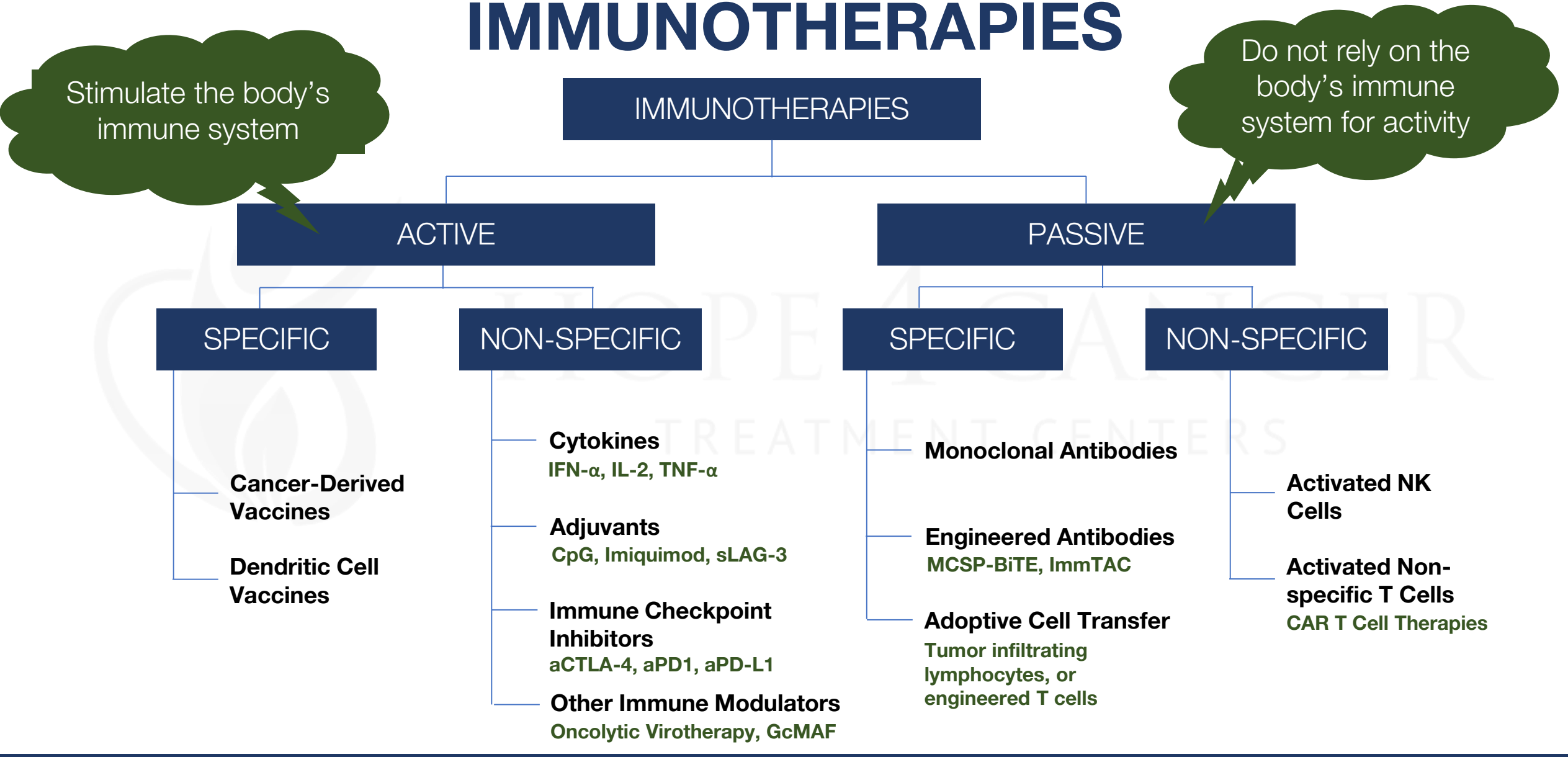
2017
Back to Back Approvals of Two Engineered CAR T Cell Therapies for ALL and B Cell Lymphoma

HALLMARKS OF CANCER

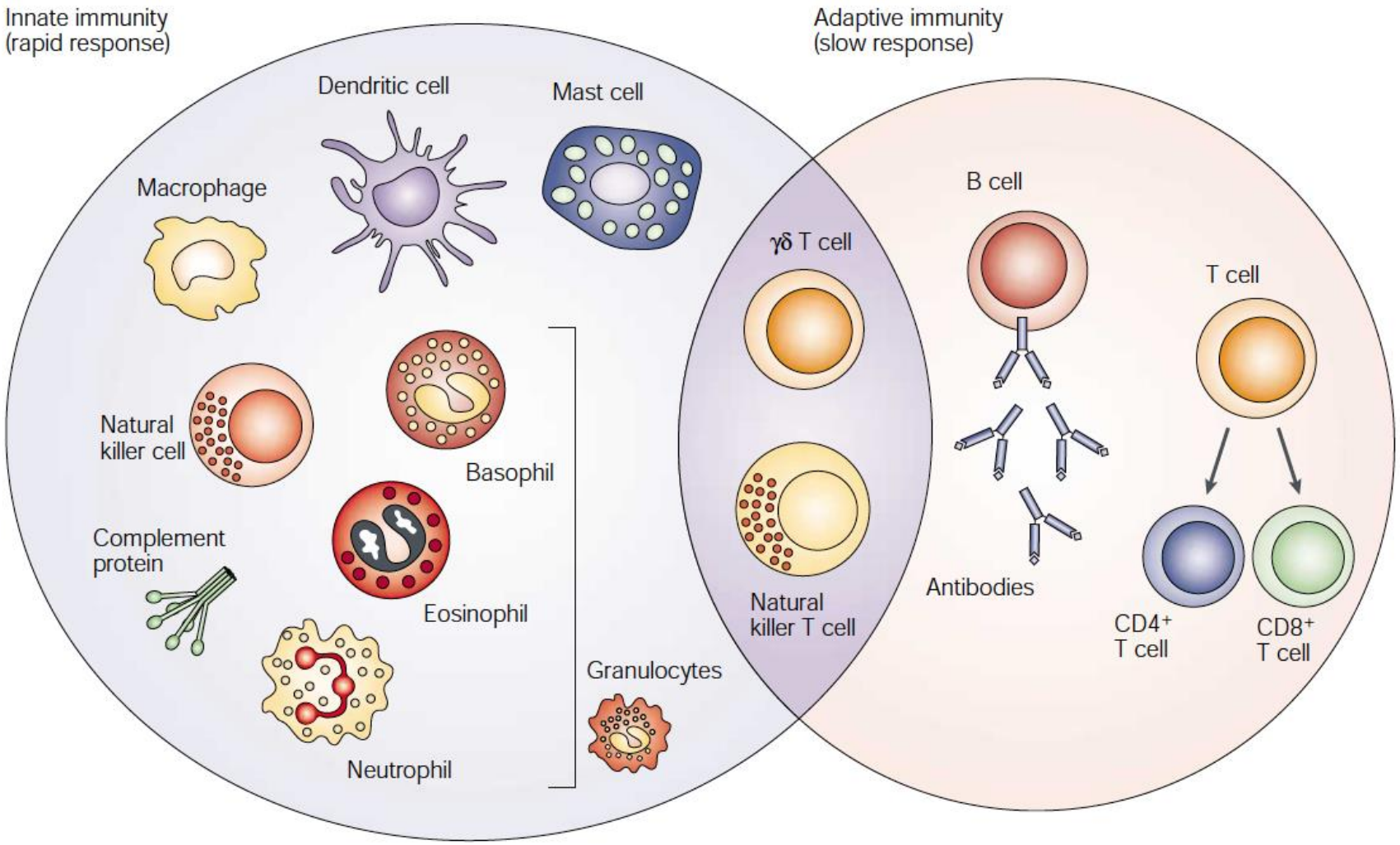
1st – 3rd Generation GcMAF Therapy Developed in Japan

THE NEW CONCEPTS IN IMMUNOTHERAPY AND IDENTIFYING DRUGGABLE TARGETS

CLASSIFICATION OF MODERN IMMUNOTHERAPIES



INNATE AND ADAPTIVE IMMUNE SYSTEMS



Dranoff, G. (2004) *Nature Reviews Cancer* 4: 11-22.

INNATE IMMUNE SYSTEM

... and present cancer-specific antigens on their surface

Cancer Cell

Macrophage

Macrophages consume cancer cells ...

CANCER VACCINES

T Cells read the antigen like a bar code and identify self vs foreign antigens

T Cell

T CELL TRANSFER THERAPIES

On identifying a foreign antigen, T cells get activated and multiply

ADAPTIVE IMMUNE SYSTEM

IMMUNE CHECKPOINT INHIBITORS

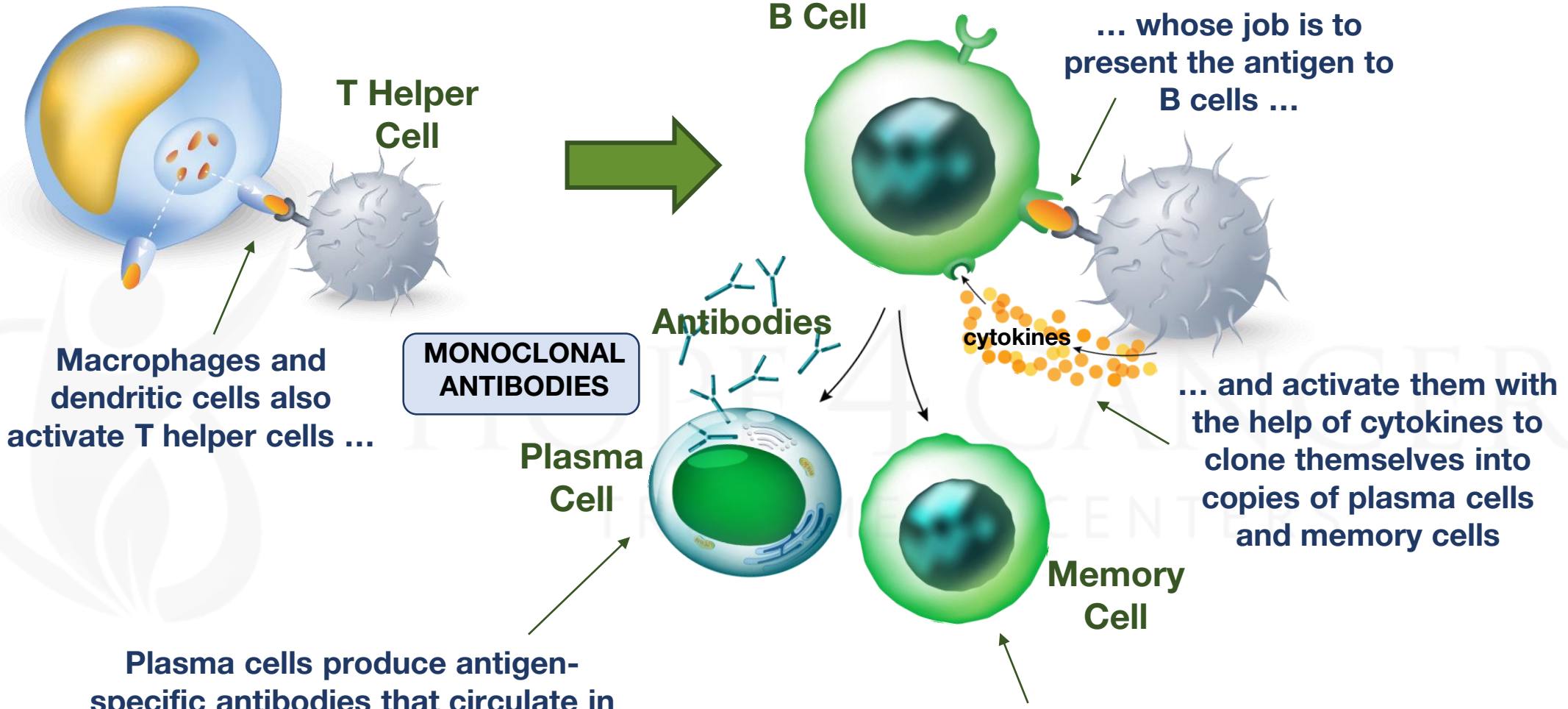
Cancer cells presenting the same antigen are detected by activated T cells which bind to them ...

... and release cytokines that kill the cancer cells

Source: Hope4Cancer Treatment Centers

ADAPTIVE IMMUNE SYSTEM

ADAPTIVE IMMUNE SYSTEM

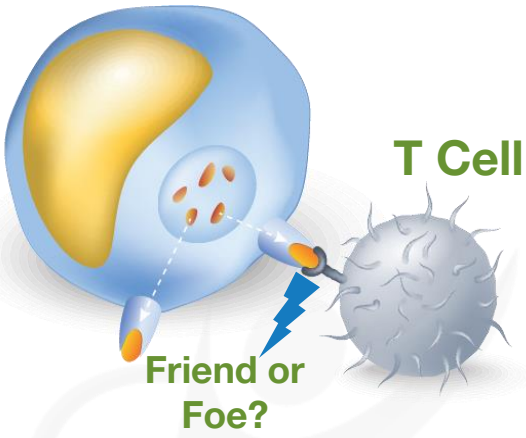


IF THE IMMUNE SYSTEM HAS IT ALL FIGURED OUT, THEN ...

WHY DO WE GET CANCER?

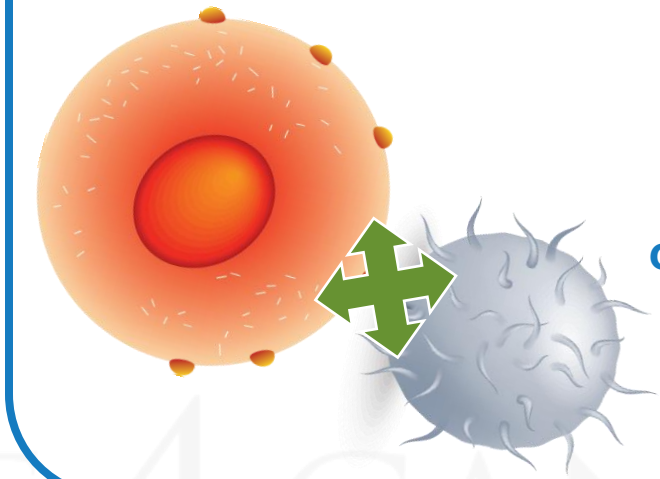
ANSWER :
Cancer Cells Are Survivors and Masters at Immune Evasion

CAN'T DIFFERENTIATE THE BAR CODE



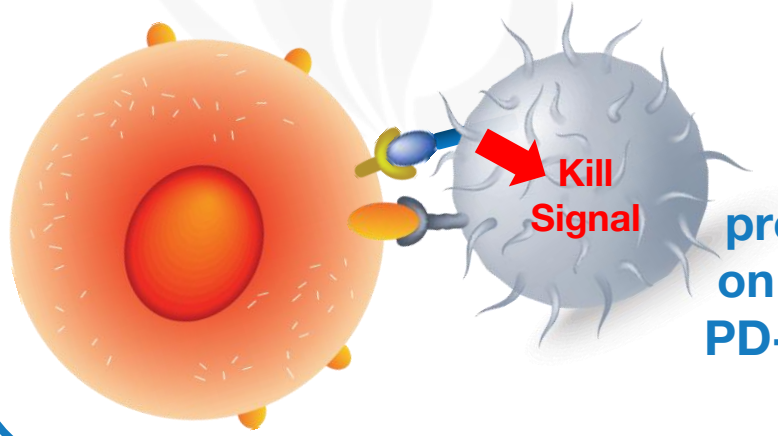
Cancer cells are very similar to normal cells, and T cells and other immune cells may not be able to distinguish differences in antigens.

LOSS OR LACK OF ANTIGENICITY



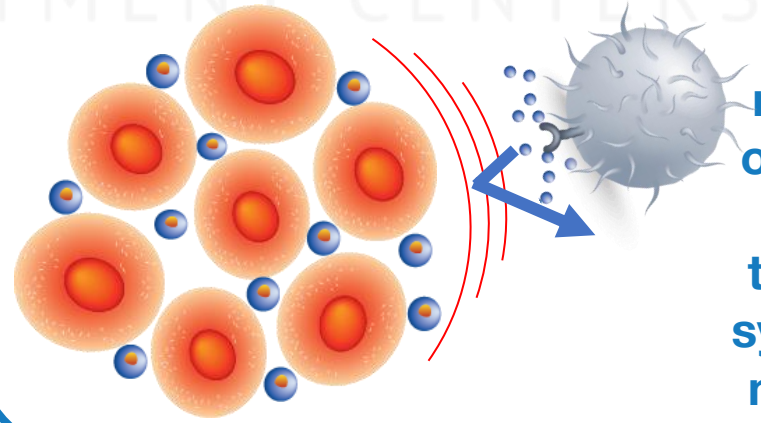
Cancer cells may not present recognizable antigens. Pluripotent cancer stem cells display virtually no antigens on their surfaces.

EXPRESSION OF IMMUNOSUPPRESSIVE ANTIGENS ON CANCER CELLS



Inflammation triggers the expression of protective antigens on cancer cells, e.g. PD-L1, that suppress T cell activity.

SUBVERSION OF IMMUNE SYSTEM BY CANCER TUMORS

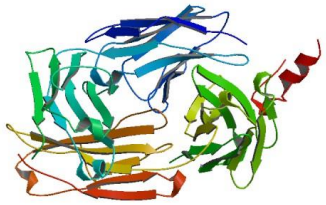


Tumors subvert macrophages and other immune cells to create its own toxic, self-defense system in the tumor micro-enviroment.

Spranger, S. and T. F. Gajewski (2018). Nat Rev Cancer **18**(3): 139-147; Source of Images: Hope4Cancer Treatment Centers

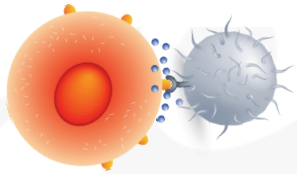
SCIENTISTS HAVE USED REDUCTIONIST APPROACHES TO IDENTIFY DRUGGABLE TARGETS

MAIN IMMUNOTHERAPY DRUG CLASSES



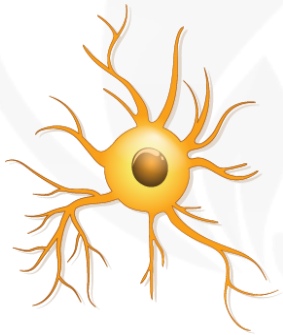
MONOCLONAL ANTIBODIES (mAb)

- Engineered antibodies that target specific antigens.
- May be used to deliver chemotherapies to target cancer cells.
- First mAb: Rituximab approved in 1997, targets CD20 on malignant B lymphocytes.



CYTOKINES

- Substances released by T cells and other immune cells to kill cancer cells.
- First cytokine: IFN-α approved for the treatment of cancer in 1986.



AUTOLOGOUS CELL THERAPY / CANCER VACCINES

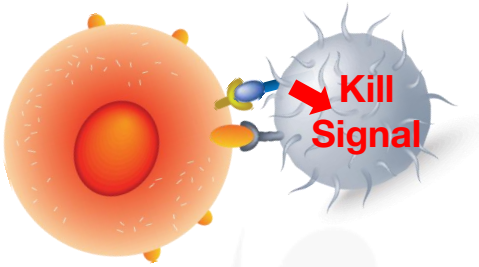
- Immature antigens presenting cells extracted from the body are engineered to contain a cancer-specific antigen and reintroduced as a vaccine.
- First vaccine: Sipuleucel-T approved in 2010 for prostate cancer, personalized.

ONCOLYTIC VIROTHERAPIES

- Uses of viruses' ability to locate, infect, and kill cancer cells.
- First genetically unmodified oncolytic virotherapy: Riga virus approved in 2004; Amgen's T-VEC was the first engineered oncolytic virotherapy.

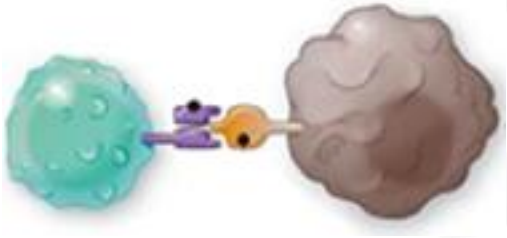
Source: Hope4Cancer Treatment Centers

MAIN IMMUNOTHERAPY DRUG CLASSES



IMMUNE CHECKPOINT INHIBITORS (ICIs)

- Antibodies engineered to bind to ligands on cancer cells, or block receptors on T cells that inhibit their ability to kill cancer cells.
- ICIs are not personalized and can be mass-manufactured as a drug.
- First approvals: Ipilimumab (Yervoy) – CTLA-4 Inhibitor; Nivolumab (Opdivo) – PD1 Inhibitor.



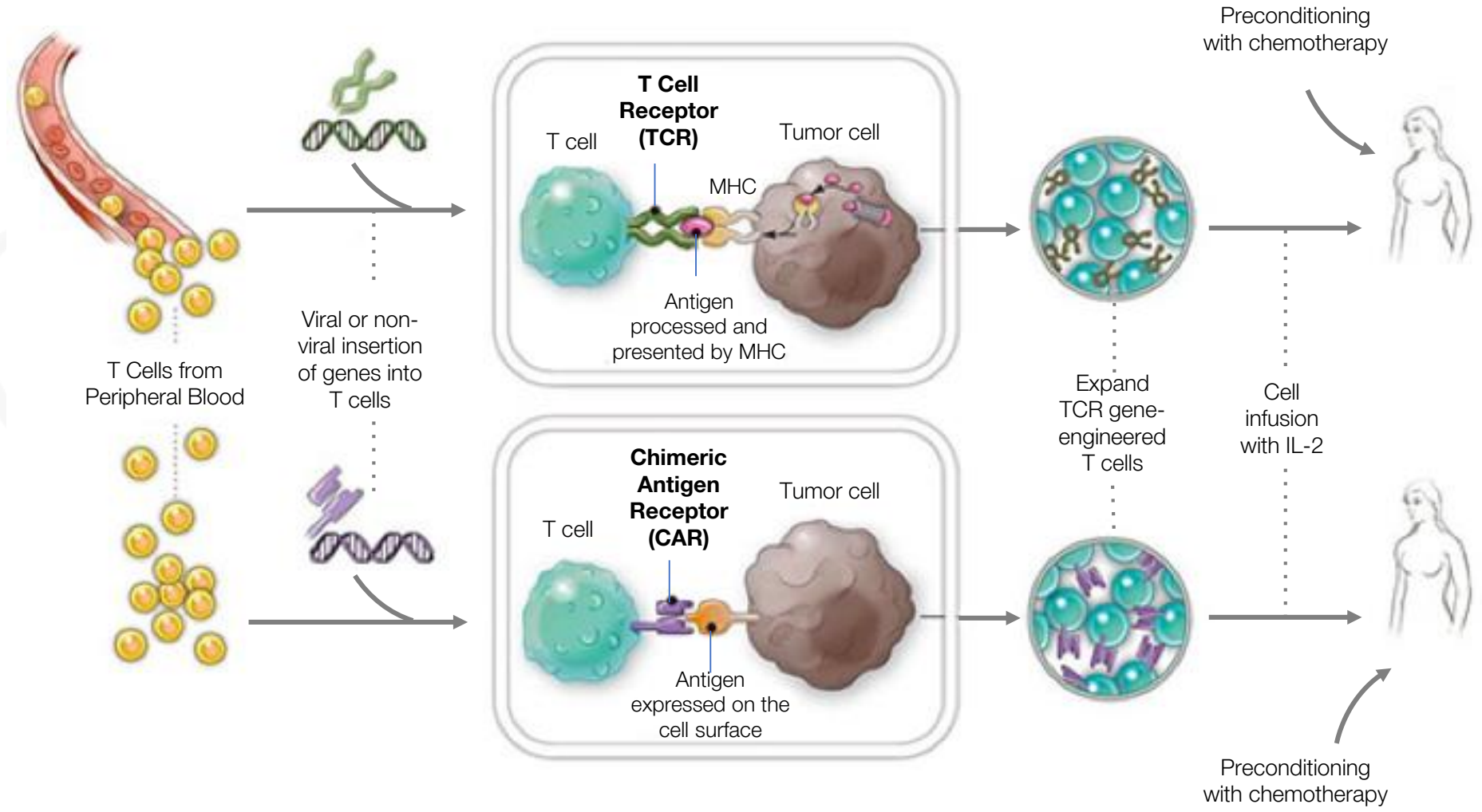
ADOPTIVE T CELL TRANSFER: TCR AND CAR T CELL THERAPIES

- Personalized therapies based on modifying T cells from patient.
- Introduction of engineered chimeric antigen receptor (CAR), or high avidity T cell receptor (TCR), into T cells.
- Amplification of T cells in laboratory.
- Pre-treatment of patient with chemotherapy to kill immune system cells.
- Transfer of CAR / TCR containing T cells to patient.

Image Source: Hope4Cancer Treatment Center, National Cancer Institute

TCR & CAR T-CELL THERAPIES

ENGINEERED T CELL RECEPTORS FOR PERSONALIZED MEDICINE



TCRs use naturally occurring receptors that can recognize antigens inside the tumor cells.

CARs use portions of synthetic antibodies that can recognize specific antigens only on the surface of the cells.

Source: National Cancer Institute website

IMMUNOTHERAPY:

HYPE VS. REALITY?

CANCER MOONSHOT 2020

Dr. Patrick Soon-Shiong
Richest Doctor in the World

"Soon-Shiong touted "clinical breakthroughs," but as proof, pointed to a lone research poster, documenting that tumors shrank in one patient after experimental therapy."

Source: https://www.statnews.com/2017/02/14/moonshot-soon-shiong-investigation/

IMMUNOTHERAPY ADVERSE EVENTS

IS IT TRULY THE POST-CHEMO BREAKTHROUGH YET?

Immune CI Drugs (Stage 3 / 4 Melanoma)	Median Progression-Free Survival (months)	% Patients With Grade 3/4 Adverse Events (Severe/Life-threatening/Impairing)
Group 1: Opdivo Only (N=315)	2.9	16.3% (7.7%*)
Group 2: Yervoy Only (N=315)	6.9	27.3% (14.8%*)
Group 3: Opdivo + Yervoy (N=315)	11.5	55.0% (36.4%*)

Larkin et al. N. Eng. J. Med. 373, 23, 2015.

OUTLOOK · 20 DECEMBER 2017 · CORRECTION 12 JANUARY 2018

The struggle to do no harm in clinical trials

What lessons are being learnt from studies that went wrong?

Recent attempts at combination immunotherapies have led to several deaths in clinical trials.

"These agents can produce autoinflammatory responses that ***we know shockingly little about …***"

- Dr. Jeffrey Weber
Deputy Director, Perlmutter Cancer Center
New York University Langone Medical Center

Source: https://www.nature.com/articles/d41586-017-08705-4

OUTLOOK · 20 DECEMBER 2017 · CORRECTION 12 JANUARY 2018

The struggle to do no harm in clinical trials

What lessons are being learnt from studies that went wrong?

Recent attempts at combination immunotherapies have led to several deaths in clinical trials.

"On balance, immunotherapy's risks don't outweigh the potential benefits for cancer patients. But we also need to be very careful when giving these therapies, **because some individuals are going to suffer serious toxicities that we can't reverse**."

- Dr. Harriet Kluger
Medical Oncologist, Yale Cancer Center

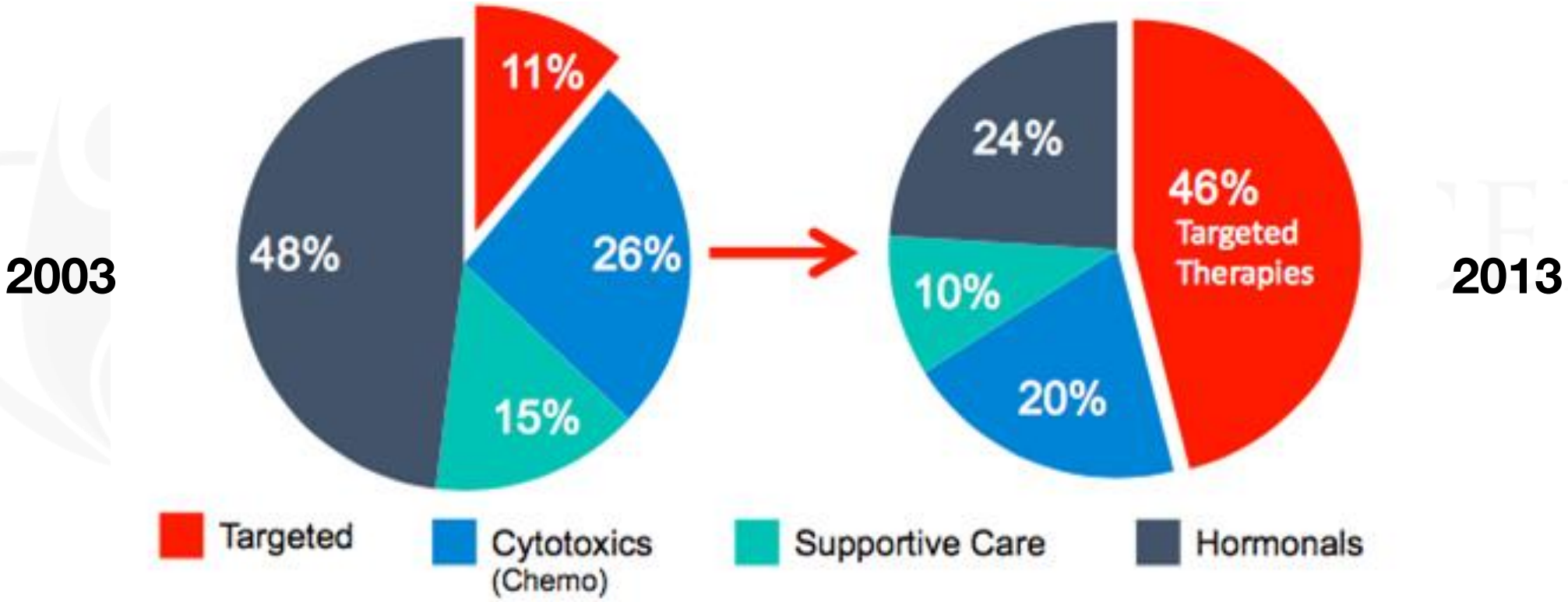
Source: https://www.nature.com/articles/d41586-017-08705-4


THE MARKET HAS DRIVEN
ACCELERATED GROWTH
WITH A MAJOR SHIFT UNDERWAY
FROM CHEMOTHERAPY TO
IMMUNOTHERAPY/TARGETED THERAPIES

ONCOLOGICAL TREATMENT MODALITIES

SHIFT IN EMPHASIS TO TARGETED + IMMUNO THERAPIES

(SALES PERCENT)

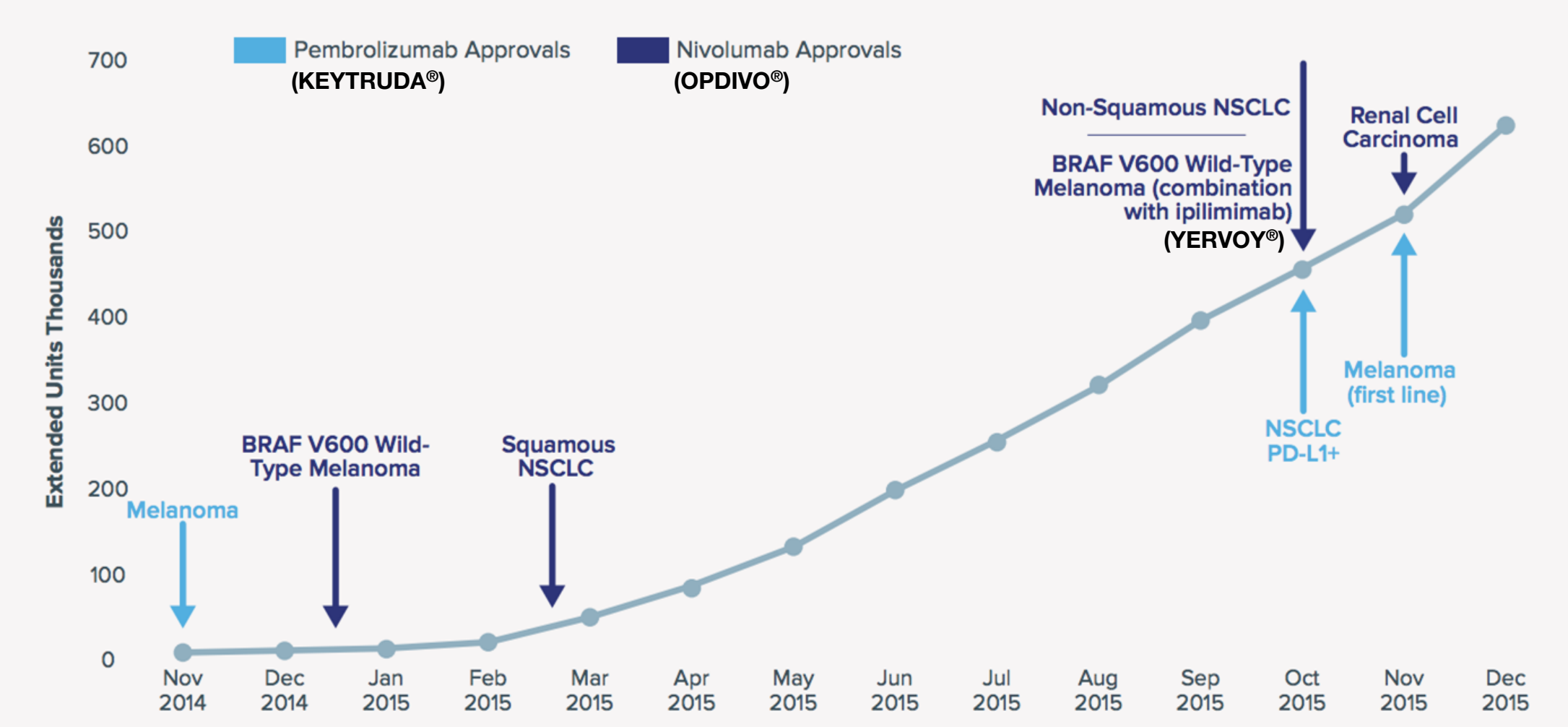


However, a majority of cancer patients (68.8%) do not currently have FDA-approved immunotherapy options.

Source: IMS Institute of Healthcare Informatics, "Innovation in Cancer Care and Implications for Health Systems: Global Oncology Trend Report, May 2014.

IMMUNOTHERAPY

RAPID UPTAKE OF IMMUNOTHERAPY PD-1 INHIBITORS IN THE U.S.



Source: U.S. FDA, Mar 2016; IMS Health, National Sales Perspective, Jan 2016; IMS Institute for Healthcare Informatics, Mar 2016.

EVEN IF THE HYPE ISN'T IMMEDIATELY REAL …

DOES IT HAVE LONG-TERM HOPE?

THE NEW IMMUNOTHERAPIES

CONCERNS SURROUNDING EFFECTIVENESS AND SAFETY

- **Serious adverse events** are common. These include autoimmune and inflammatory reactions, endocrinopathies, dermatitis, colitis, hepatitis, etc.

- **Immune evasion and resistance** make these treatments effective only in a small subset of patients. Currently, about 70% patients cannot be prescribed immunotherapies at all.

- **Hyperactivation of T cells** (adoptive T cell therapies) can spiral out of control. Autoimmune problems: unexpected organ damage, severe neurotoxicity, lowered blood pressure, patient death from treatments.

- **Cytokine storms** – overactivation of T cells can release too many cytokines causing labored breathing, rapid pulse, high fevers, decreased blood flow to organs, coma.

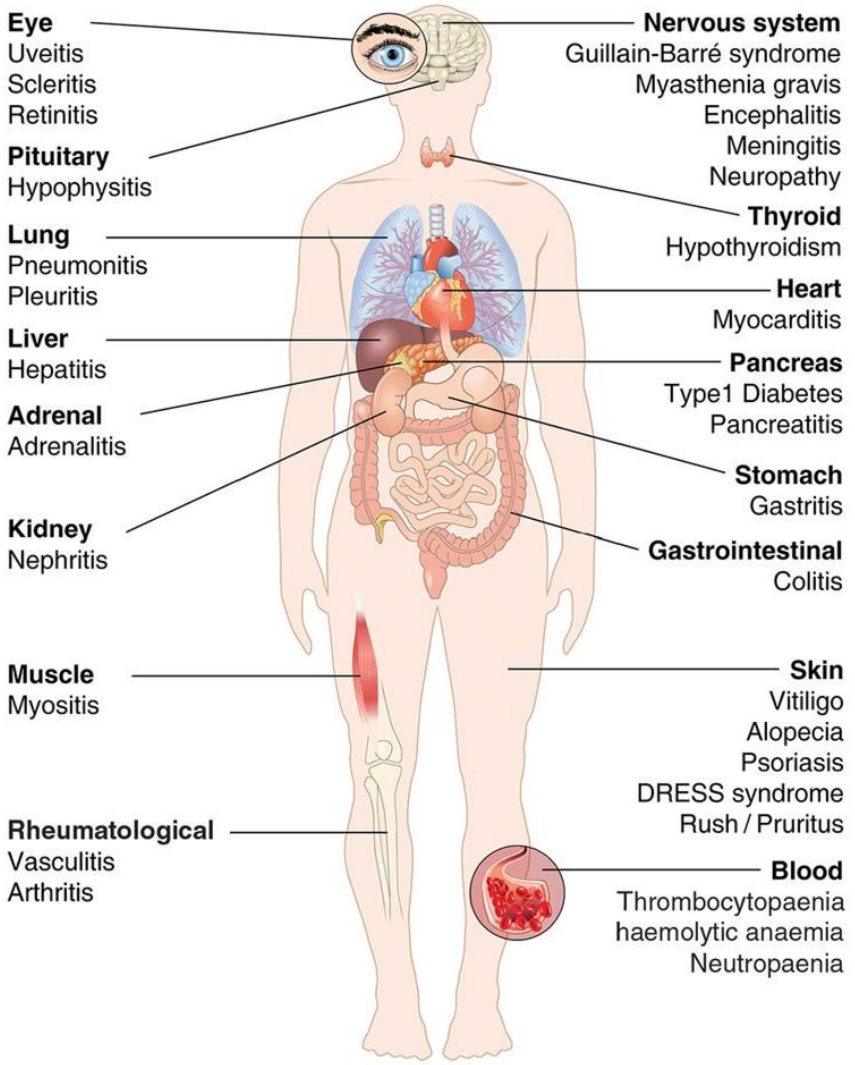
- **Pre-administration of chemotherapy/radiation needed** resulting in the killing of the existing immune system to clear the path for the engineered T cells.

- **Poor penetration of engineered immune agents into solid tumors.**

Gilda Varricchi et al. ESMO Open 2017;2:e000247 | June, C. H.; Warshauer, J. T.; Bluestone, J. A., *Nat Med* **2017,** *23* (5), 540-547.

IMMUNE CHECKPOINT INHIBITORS (ICIs)

ADVERSE EVENTS ASSOCIATED WITH ICIs (PD-1 and CTLA4 INHIBITORS)



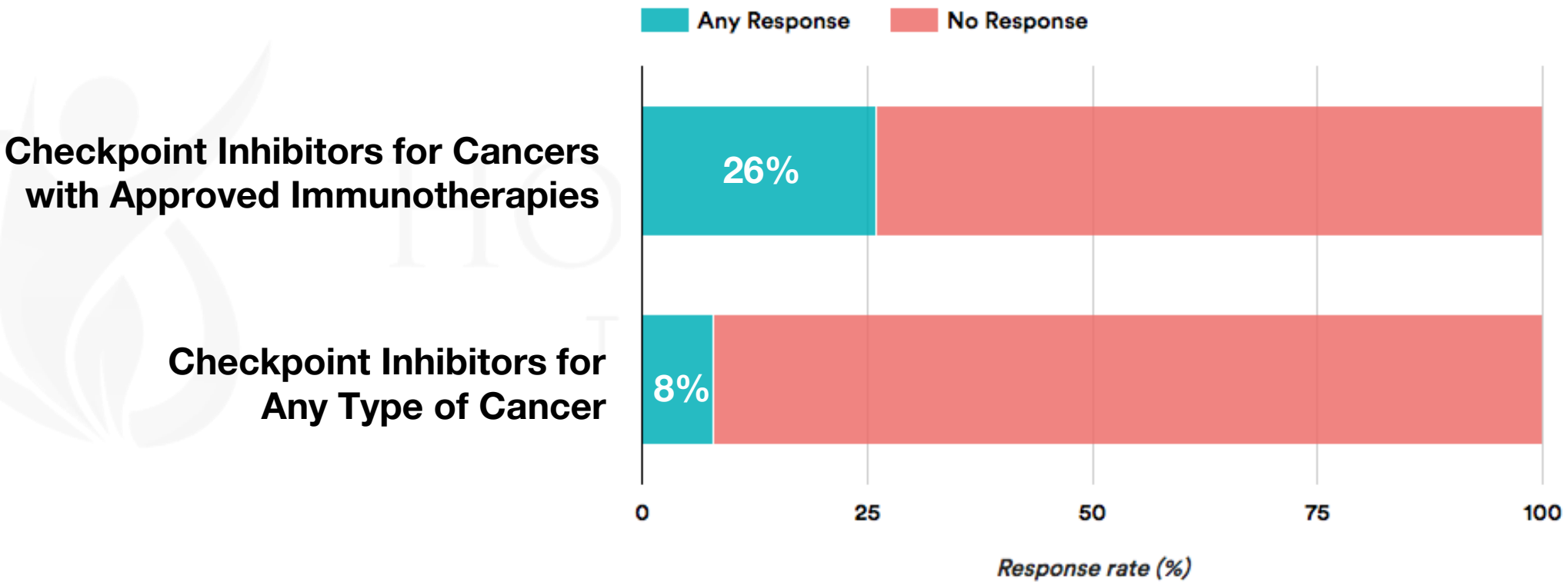
- Immune checkpoints are part of the body's protective mechanism to maintain immunological homeostasis.
- Their blockage with Immune Checkpoint Inhibitors (ICIs) can lead to unpredictable autoimmune and inflammatory side effects, a.k.a. "Immune Related Adverse Events (IRAE)."
- Endocrinopathies occur in 6-8% patients on causing irreversible toxicities (targets: thyroid and pituitary).

FDA APPROVED ICIs:
CTLA-4 Inhibitor: Ipilimumab/Yervoy® (2011)
PD-1 Inhibitors: Pembrolizumab/Keytruda®, Nivolumab/Opdivo® (2014); Atezolizumab/Tecentriq® (2016)

Gilda Varricchi et al. ESMO Open 2017;2:e000247 | June, C. H.; Warshauer, J. T.; Bluestone, J. A., *Nat Med* **2017,** *23* (5), 540-547.

RESPONSE TO ICI IMMUNOTHERAPY DRUGS

Measured Response = Tumor Shrinkage



68.8% of cancer patients remain untreatable with the latest immunotherapies
Over 90% of patients will not benefit from the current state-of-art in immunotherapy

Gay, N.; Prasad, V. (2017) Stat News: www.statnews.com/2017/03/08/immunotherapy-cancer-breakthrough/

THE NEW IMMUNOTHERAPIES

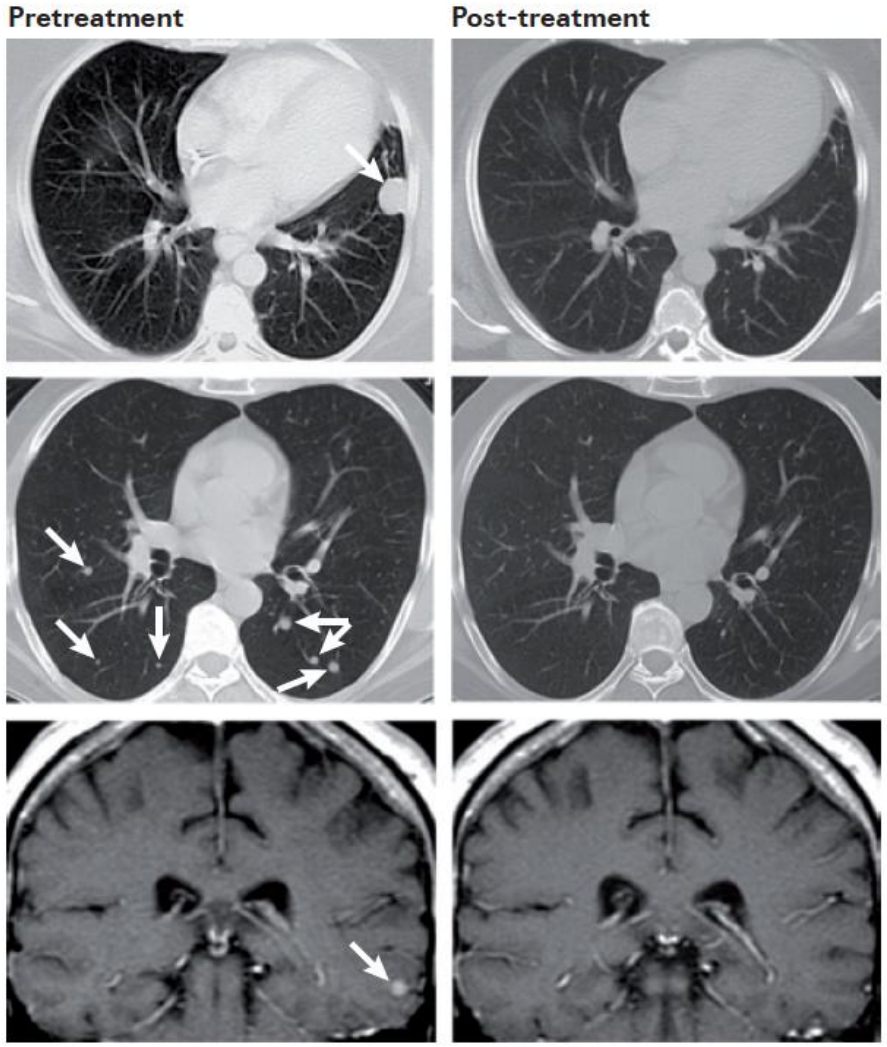
SURVIVAL AND COST OF TREATMENT

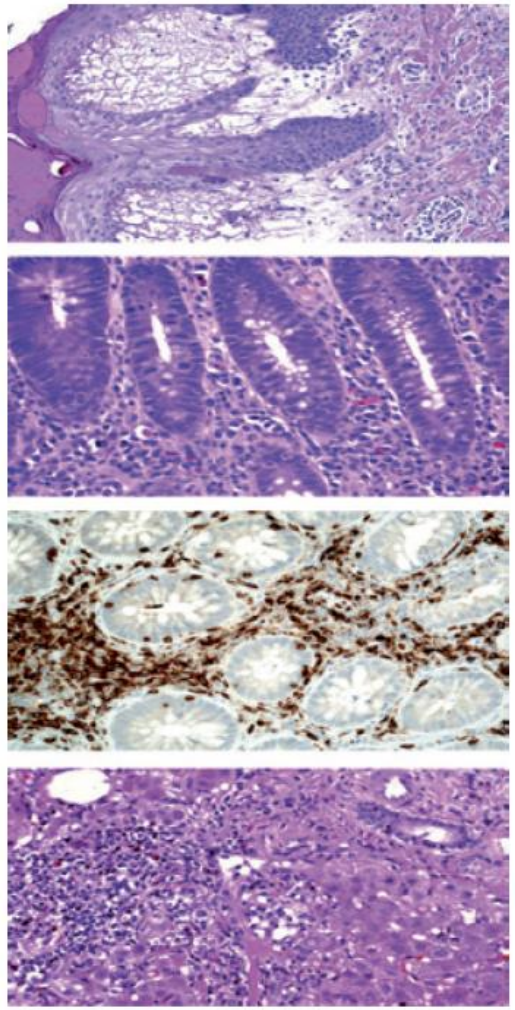
- **Extension of survival time** has been relatively limited based on clinical studies, e.g.
  - Sipuleucel-T extends ***overall survival*** of prostate cancer patients by approximately 4 months over placebo.
  - Median ***progression-free survival*** for immune checkpoint inhibitors, Ipilimumab was 6.9 months and Nivolumab was 2.9 months.
  - **CAR T Therapy** for B-cell acute ALL showed impressive results with 44/53 patients reporting remission with a median survival of over 1 year. Against B Cell Lymphoma, 50% patients went into remission, while 30% showed partial response.
    - Common side effects: Neutropenia, anemia, potentially fatal cytokine release syndrome (13% of patients), neurological events (30% of patients).
    - Treatment-related deaths became a serious concern throughout clinical studies.
    - Once stabilized, costs are expected to go up to $600,000 - $750,000 for a single treatment.

Gilda Varricchi et al. ESMO Open 2017;2:e000247 | June, C. H.; Warshauer, J. T.; Bluestone, J. A., *Nat Med* **2017,** *23* (5), 540-547.

IMMUNE CHECKPOINT INHIBITORS

ADVERSE EVENTS FROM CTLA-4 INHIBITOR, IPILIMUMAB





Dermatitis

Colitis

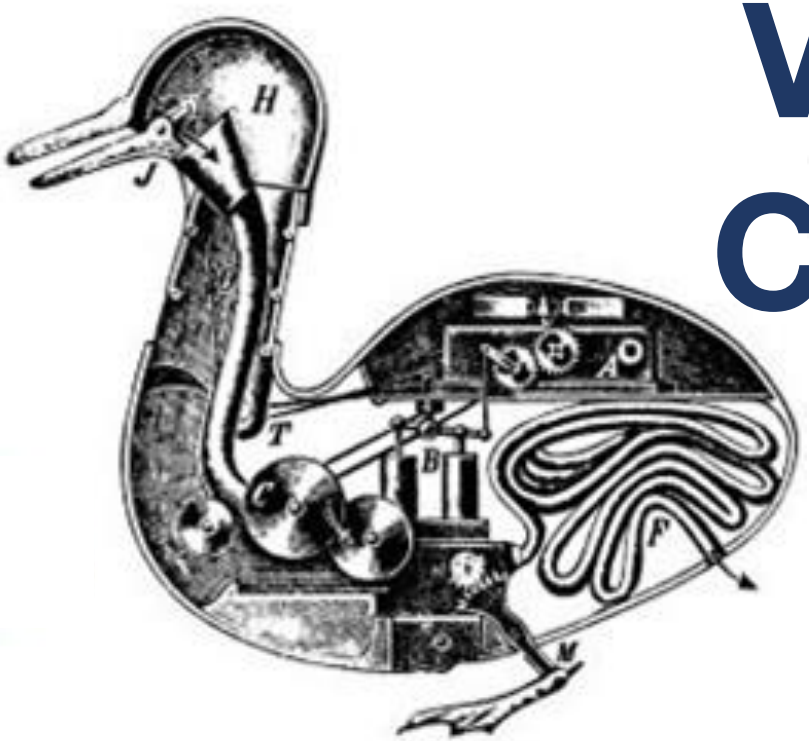
Colitis

Hepatitis

- 25-30% of patients develop on-target toxicities with extended doses of anti-CTLA-4 therapy.
- Commonly affected areas include the skin (dermatitis) and the colon (colitis), and less frequently, the liver, lungs, pituitary, and thyroid glands.
- Each dose of Ipilimumab costs US $30,000.

Pardoll, D. M., *Nat Rev Cancer* **2012,** *12* (4), 252-64; Phan, G.Q. et al. *Proc. Natl. Acad. Sci.* **2003,** *100*, 8372-8377.

TREATMENT PHILOSOPHY



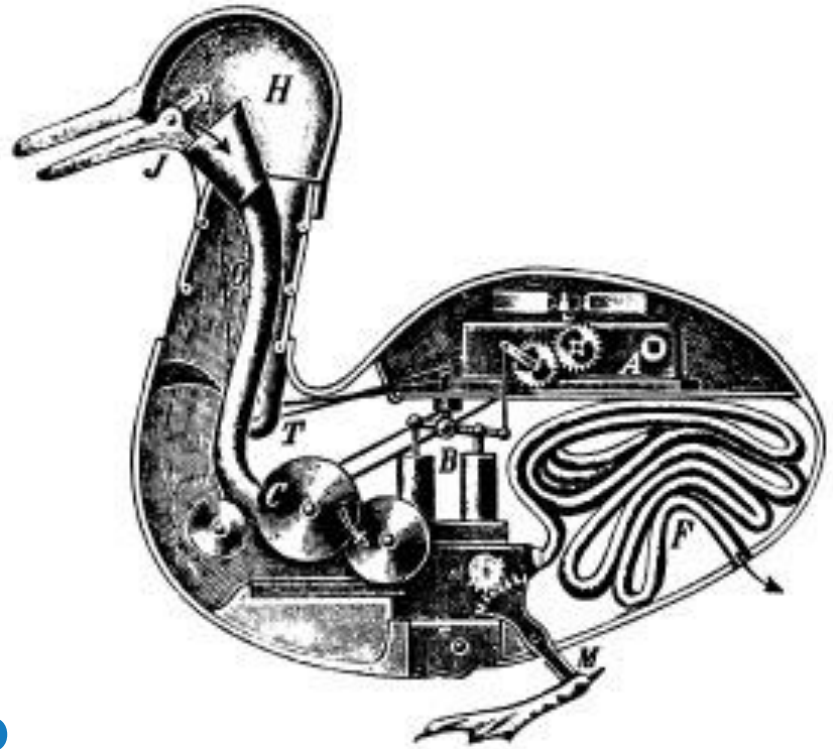
REDUCTIONISM VS. HOLISM/ COMPLEXITY THEORIES?

REDUCTIONISM

Ontological reductionism: A belief that the whole of reality consists of a minimal number of parts.

Methodological reductionism: The scientific attempt to provide explanation in terms of ever smaller entities.

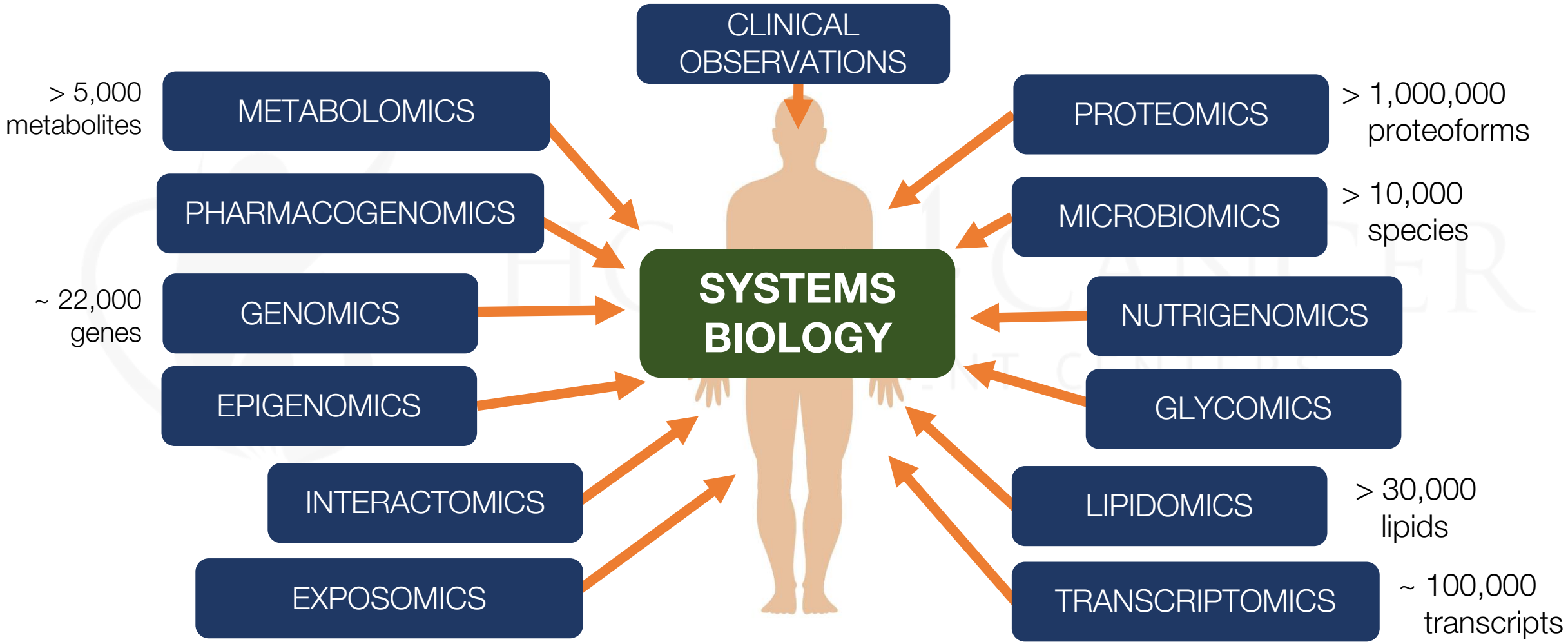
The successes of reductionism in simpler inanimate concepts has made us addicted to forcing the process in all scenarios, including human biology and medicine.



Descartes “automata” concept for non-human animals

Source of definitions: https://en.wikipedia.org/wiki/Reductionism

PERSONALIZED MEDICINE?



Source: Hope4Cancer Treatment Centers

THE IMMUNOTHERAPY DILEMMA

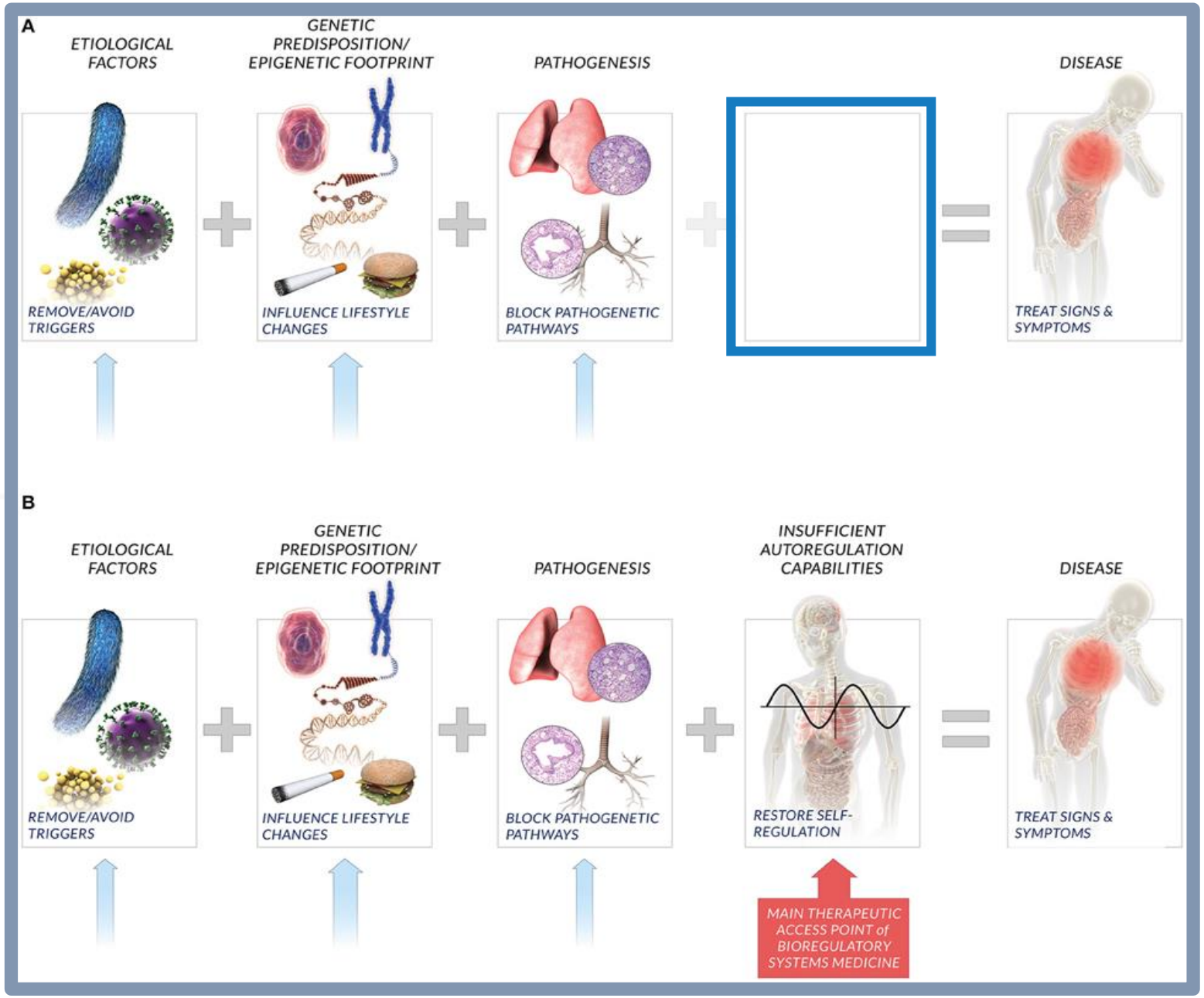
Today's Immunotherapy revolution began with the reluctant admission that a larger view of the human body was necessary to treat cancer, but has defaulted back to a reductionist philosophy that is destined to fail.

The market and public perception is used to reductionism – therefore, it is necessary.

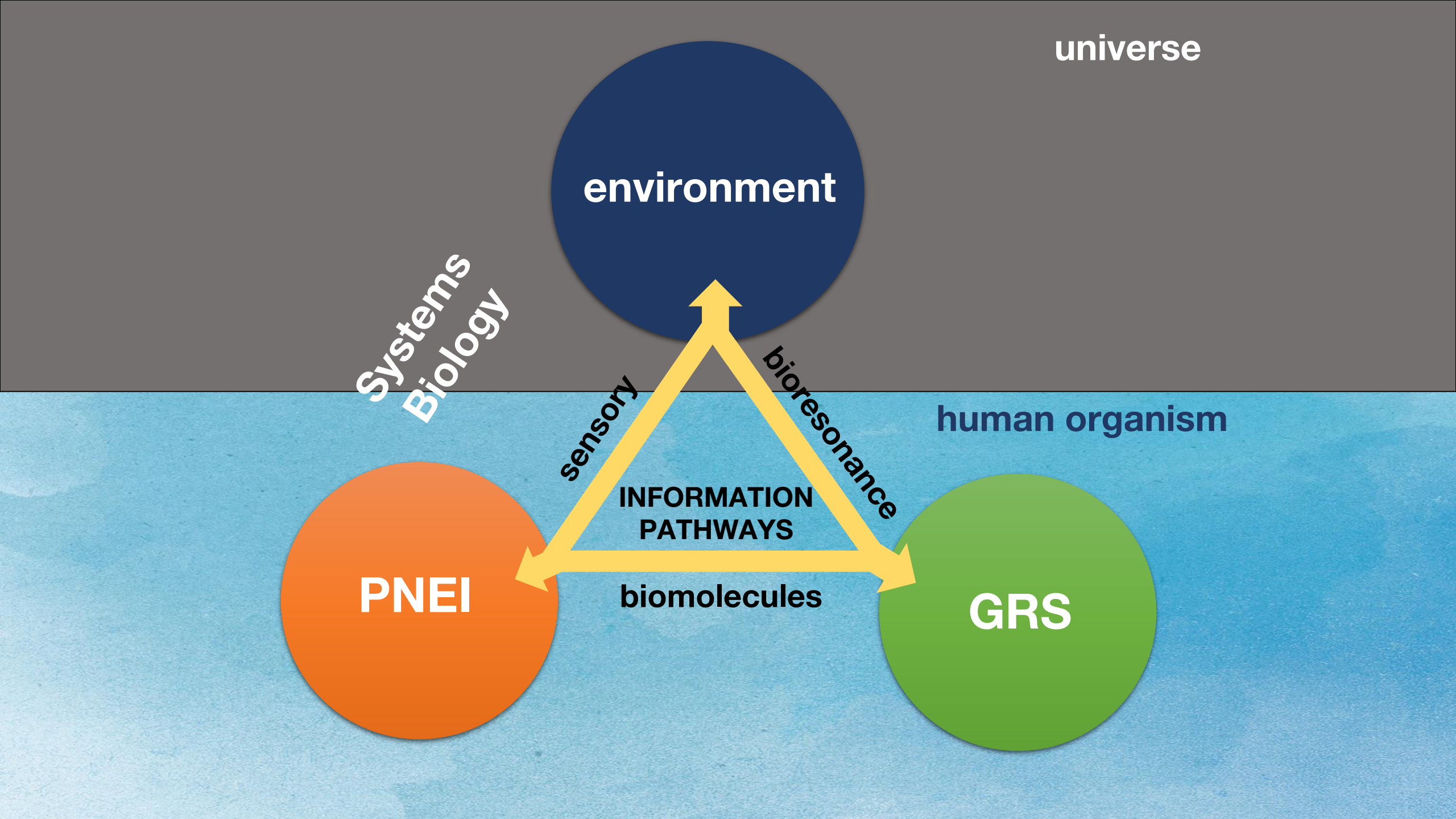
It doesn't mean it is the right approach.

REDUCTIONIST

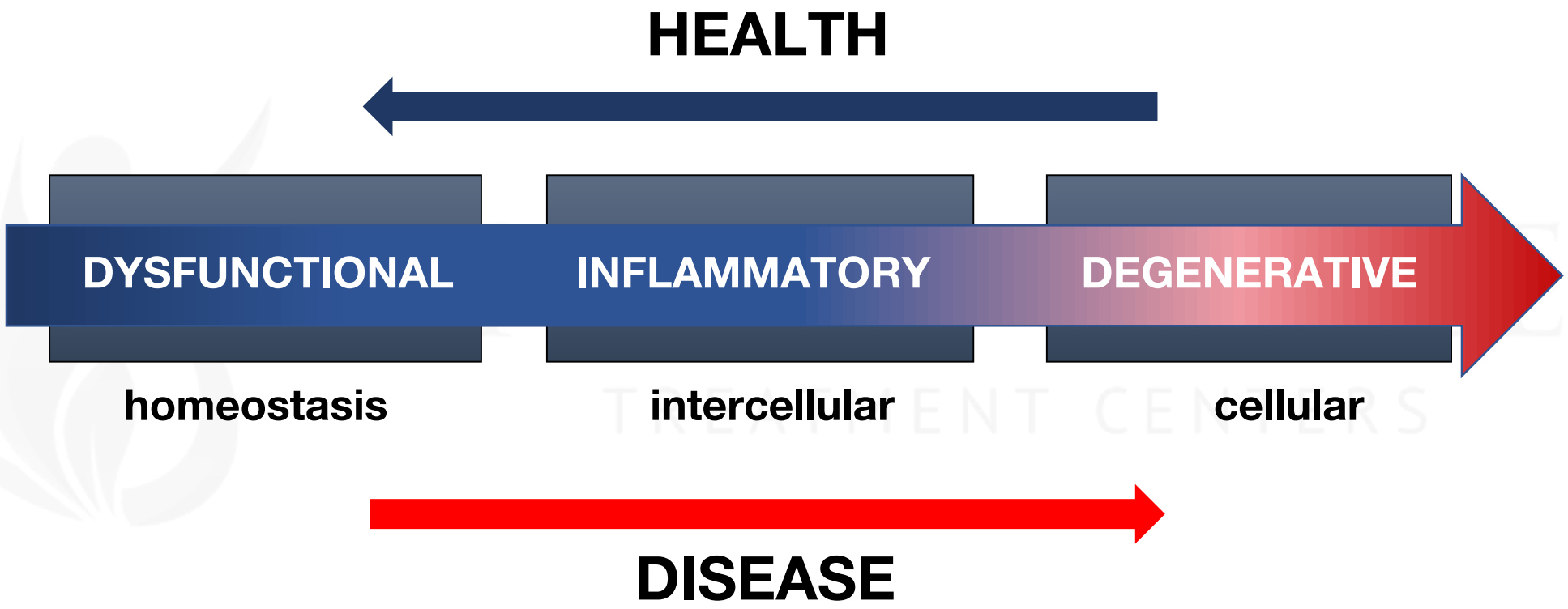
HOLISTIC



Goldman AW, Burmeister Y, Cesnulevicius K, et al. *Frontiers in Physiology*. 2015;6:225.


universe
environment
Systems Biology
sensory
bioresonance
human organism
INFORMATION PATHWAYS
biomolecules
PNEI
GRS

REDUCTIONISM IGNORES THE LARGER PROCESS OF "DISEASE"



Smit, A.; O'Byrne, A. (2009). Introduction to Bioregulatory Medicine (Thieme Hardcover).

EXAMPLE: IMPACT OF MICROBIOME

CLINICAL DATA SUGGESTS THE A HOLISTIC THERAPEUTIC APPROACH WOULD WORK MUCH MORE EFFICIENTLY

- **Study 1:** Melanoma patients who responded to anti PD-1 therapy had higher within-sample diversity of their intestinal microbiome, and higher abundance of specific bacterial populations.
- **Study 2**: Eight species were found enriched in faecal samples of anti PD-1 responders, including *Bifidobacterium longum*. *Ruminococcus obeum* and *Roseburia intestinalis* were more abundant in non-responders.
- **Study 3:** More diverse intestinal microbiome observed in responders, as well as marked increase in abundance of *Akkermansia muciniphila.* Exposure to antibiotics decreased the probability of response to therapy.

In all three studies, faecal microbiota transplantation (FMT) from human anti PD-1 responders to germ-free mice led to enhanced antitumor immunity compared to mice that received the FMT from non-responders.

(1) Gopalakrishnan, V. et al., *Science* **2018**, *359*, 97-103. | (2) Matson, V. et al. *Science* **2018, *359,*** 104-108**. | (3)** Routy, B. et al. *Science* **2018, *359,*** 91-97.

A REDUCTIONIST'S PERSPECTIVE OF CURRENT IMMUNOTHERAPY CHALLENGES AND THEIR SOLUTIONS

LISTED CHALLENGES

- Efficacy is often unpredictable
- Difficulty identifying clinically significant biomarkers
- Need for more predictive biomarkers
- Tumor heterogeneity impedes efficacy
- Development of resistance to drug treatment
- Need for distinct clinical study designs to evaluate efficacy
- Cancer immunotherapy drugs are expensive

SUGGESTED SOLUTIONS

- More targeted approaches to enhance efficacy and reduce toxicity
- Personalized drug combination therapies to enhance efficacy
- Immunoprevention strategies to prevent cancer and its recurrence (e.g. vaccines, targeting identified pathogens, drug induced antigen suppression, etc.)

Ventola, C. L., *Pharmacy and Therapeutics* **2017,** *42* (8), 514-521.

SUGGESTED FIX FOR SUB-PAR RESULTS

COMBINING MULTIPLE THERAPIES

- Currently 1000's of clinical trials are proposed or underway for immunotherapy agents – there are not sufficient patients to enroll.

- Many of these trials now involve either finding a company-specific patentable compound, or combination therapies:

  - **CAR T Cells + Oncolytic Virotherapy (OV)**
    (hypothesis: OVs can carry CAR T Cells into tumors they cannot penetrate)

  - **CAR T Cells + Immune Checkpoint Blockers + Angiogenesis Inhibitors (AI)**
    (hypothesis: AIs can help more successful infiltration of tumor)

<u>Predictable outcome</u>: Massive amplification of side effects, while maintaining ignorance of the larger holistic aspects of treatment necessary for recovery.

Vanneman, M.; Dranoff, G., *Nat Rev Cancer* **2012,** *12* (4), 237-51.

MULTI-TARGETED APPROACH

A PROPOSED SCHEME TO OVERCOME IMMUNE ESCAPE/RESISTANCE

STEP 1 — MODULATE TUMOR INFLAMMATION

Inhibit Innate Tumor Immunity

CSF1/CSF-1R Antagonists
CCR2/CCL2 Antagonists
Bisphosphonates
VEGF/VEGFR Antagonists

Reprogram Innate Immunity

TLR Antagonists
JAK 1/2 Antagonists
STAT3 Inhibitors
IKKβ Inhibitors
CD40 Agonists
CD47 Antagonists
IL6 Antagonists

STEP 2 — INDUCE/BOOST T CELL ANTITUMOR IMMUNITY

Deliver Tumor Antigen

Peptide
Antigen-loaded DCs
Whole Tumor Cell
Gene Therapy
(Bacterial/Viral Vectors)

Induce Immunogenic Cell Death

Chemotherapy
Radiation Therapy
Antibody-Drug Conjugates

Transfer Immunity

Adoptive Therapy with T Cells

STEP 3 — REVERSE MECHANISMS OF IMMUNE TOLERANCE

Reverse Immunosuppression

TGFβ Inhibitors
IL10 Antagonists
COX2 Inhibitors
IDO Inhibition

Block Immune Checkpoints

Anti PD-1/PD-L1 Antibodies
Anti-CTLA-4 Antibodies

Theoretical construct with very poor likelihood of therapeutic or economic success.

Beatty, G. L.; Gladney, W. L., *Clin Cancer Res* **2015,** *21* (4), 687-92.

THE SEVEN KEY PRINCIPLES OF CANCER THERAPY™

A Holistic, Science-Based Approach to Treating Cancer

THE TEN HALLMARKS OF CANCER

SCOPE REMAINS TOO WIDE FOR NEW TARGETED APPROACH

- INVADES AND SPREADS
- BYPASSES BODY'S CHECKS AND BALANCES
- EVADES IMMUNE SYSTEM
- RESISTS CELL DEATH
- CHANGES METABOLISM
- CAN MULTIPLY INDEFINITELY
- DESTABILIZES DNA
- CAUSES INFLAMMATION
- GROWTH SIGNALS OUT OF CONTROL
- CREATES BLOOD VESSELS TO FEED TUMOR

TREAT THE CANCER

+

TREAT THE TERRAIN

Hanahan, D.; Weinberg, R. A. (2011) *Cell* **144** (5): 646–674; Hanahan D, Weinberg RA (2000) *Cell* **100** (1): 57–70.

CANCER TERRAIN

Physio-Emotional Factors

Compromised Immune System

Aging

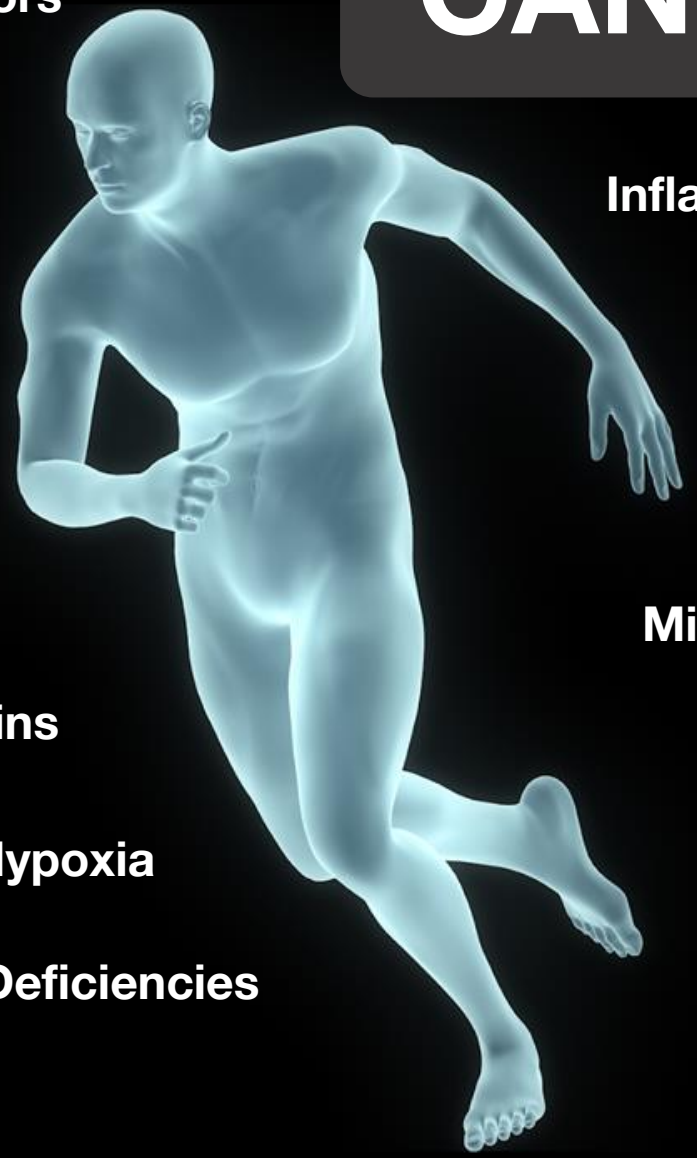
Acid / Alkaline Balance

Pre-existing Genetic Factors

Toxins

Hypoxia

Mineral Deficiencies



Inflammatory Factors

Dental Work

Hormonal Balance

Microbiome Balance

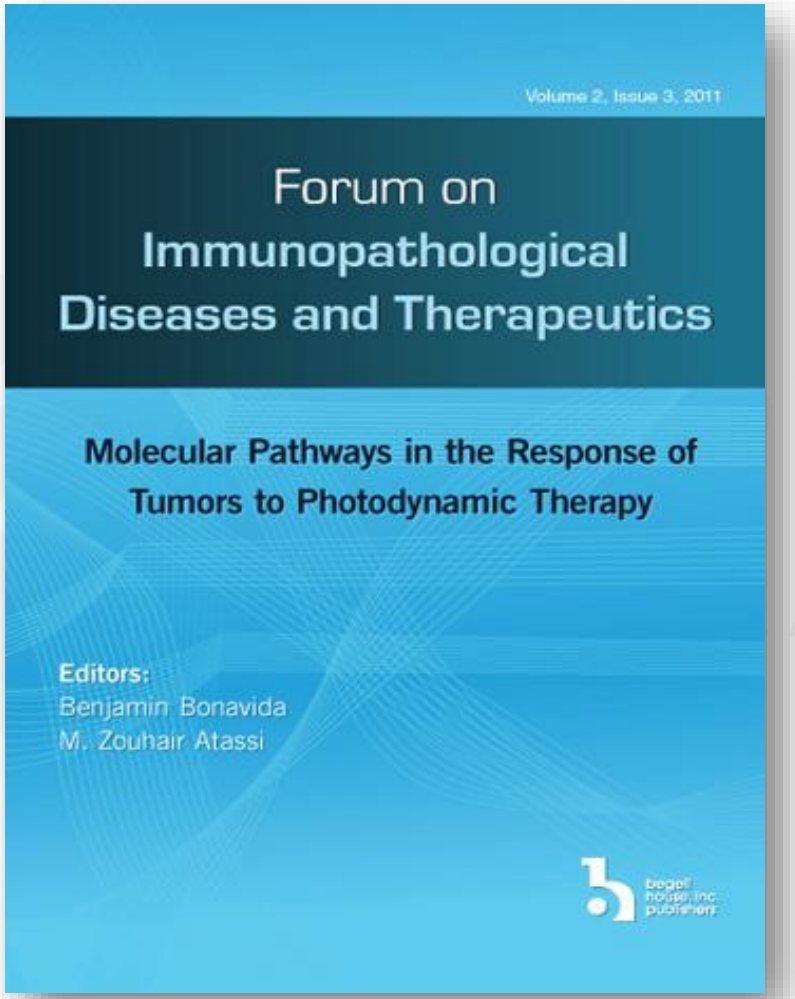
Free Radicals

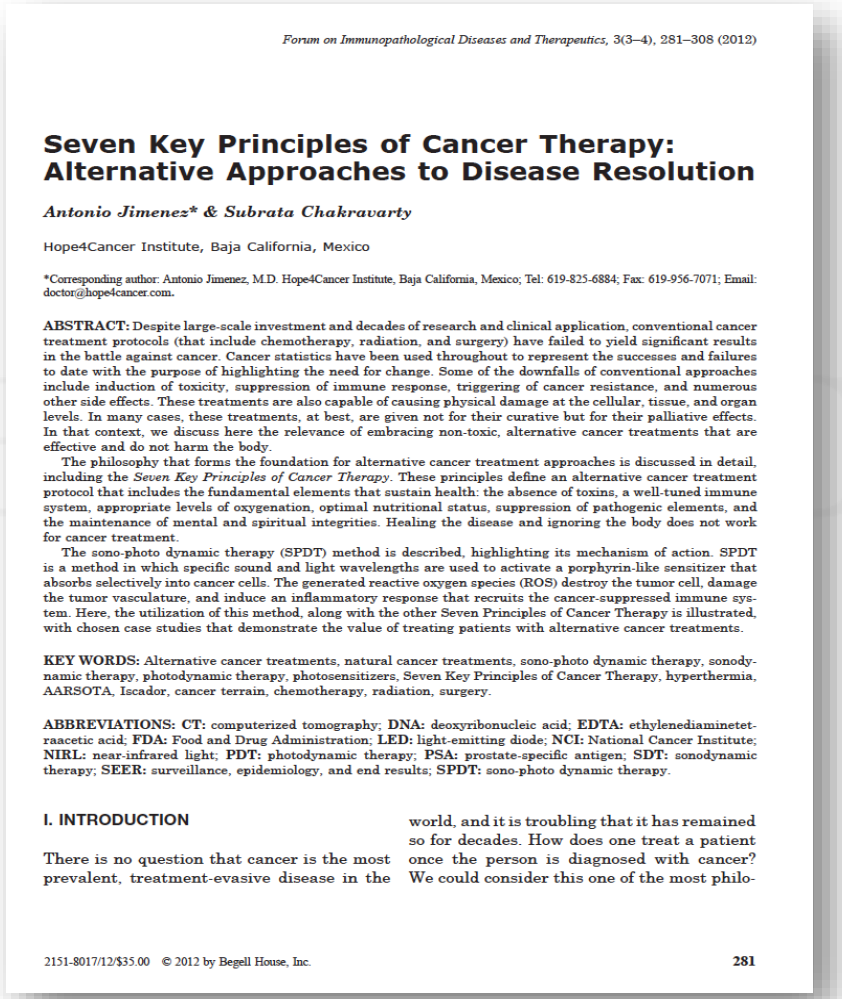
Nutritional Status

Metabolic Factors

Adapted From: Jimenez, A.; Chakravarty, S. *Forum on Immunopathol. Dis. Ther.* **2012,** *3* (3-4), 281-308.

THE SEVEN KEY PRINCIPLES OF CANCER THERAPY





Forum on Immunopathological Diseases and Therapeutics, 3(3–4), 281–308 (2012)

Seven Key Principles of Cancer Therapy: Alternative Approaches to Disease Resolution

Antonio Jimenez & Subrata Chakravarty*

Hope4Cancer Institute, Baja California, Mexico

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ABSTRACT: Despite large-scale investment and decades of research and clinical application, conventional cancer treatment protocols (that include chemotherapy, radiation, and surgery) have failed to yield significant results in the battle against cancer. Cancer statistics have been used throughout to represent the successes and failures to date with the purpose of highlighting the need for change. Some of the downfalls of conventional approaches include induction of toxicity, suppression of immune response, triggering of cancer resistance, and numerous other side effects. These treatments are also capable of causing physical damage at the cellular, tissue, and organ levels. In many cases, these treatments, at best, are given not for their curative but for their palliative effects. In that context, we discuss here the relevance of embracing non-toxic, alternative cancer treatments that are effective and do not harm the body.

The philosophy that forms the foundation for alternative cancer treatment approaches is discussed in detail, including the *Seven Key Principles of Cancer Therapy*. These principles define an alternative cancer treatment protocol that includes the fundamental elements that sustain health: the absence of toxins, a well-tuned immune system, appropriate levels of oxygenation, optimal nutritional status, suppression of pathogenic elements, and the maintenance of mental and spiritual integrities. Healing the disease and ignoring the body does not work for cancer treatment.

The sono-photo dynamic therapy (SPDT) method is described, highlighting its mechanism of action. SPDT is a method in which specific sound and light wavelengths are used to activate a porphyrin-like sensitizer that absorbs selectively into cancer cells. The generated reactive oxygen species (ROS) destroy the tumor cell, damage the tumor vasculature, and induce an inflammatory response that recruits the cancer-suppressed immune system. Here, the utilization of this method, along with the other Seven Principles of Cancer Therapy is illustrated, with chosen case studies that demonstrate the value of treating patients with alternative cancer treatments.

KEY WORDS: Alternative cancer treatments, natural cancer treatments, sono-photo dynamic therapy, sonodynamic therapy, photodynamic therapy, photosensitizers, Seven Key Principles of Cancer Therapy, hyperthermia, AARSOTA, Iscador, cancer terrain, chemotherapy, radiation, surgery.

ABBREVIATIONS: CT: computerized tomography; **DNA:** deoxyribonucleic acid; **EDTA:** ethylenediaminetetraacetic acid; **FDA:** Food and Drug Administration; **LED:** light-emitting diode; **NCI:** National Cancer Institute; **NIRL:** near-infrared light; **PDT:** photodynamic therapy; **PSA:** prostate-specific antigen; **SDT:** sonodynamic therapy; **SEER:** surveillance, epidemiology, and end results; **SPDT:** sono-photo dynamic therapy.

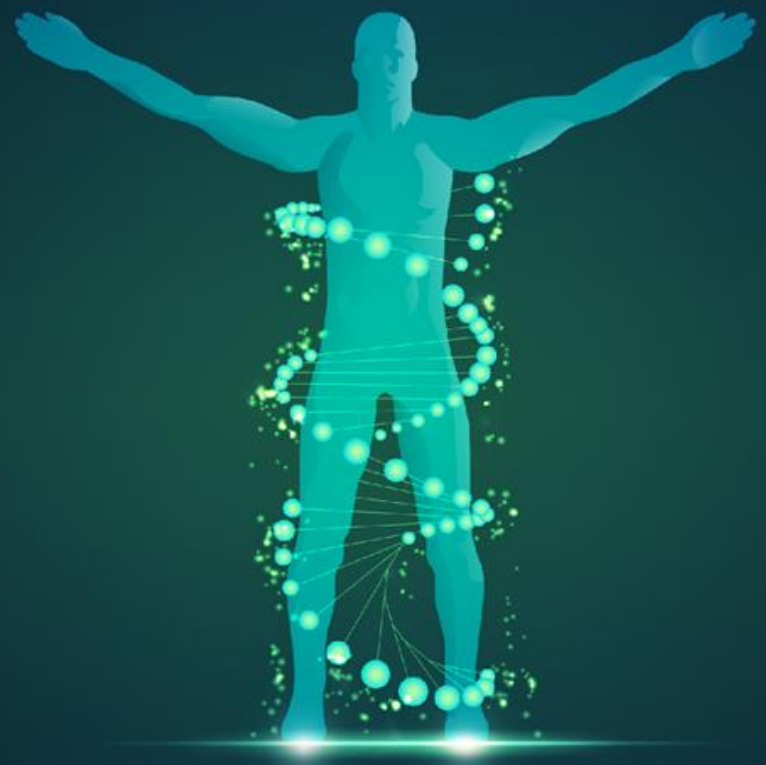
I. INTRODUCTION

There is no question that cancer is the most prevalent, treatment-evasive disease in the world, and it is troubling that it has remained so for decades. How does one treat a patient once the person is diagnosed with cancer? We could consider this one of the most philo-

2151-8017/12/$35.00

Jimenez, A.; Chakravarty, S. *Forum on Immunopathological Diseases and Therapeutics* **2012,** *3* (3-4), 281-308.

7 KEY PRINCIPLES OF CANCER THERAPY™



- NON-TOXIC CANCER THERAPIES
- IMMUNO MODULATION
- O_2 OXYGENATION
- FULL SPECTRUM NUTRITION
- RESTORE MICROBIOME
- DETOXIFICATION
- EMOTIONAL AND SPIRITUAL HEALING

7 KEY PRINCIPLES OF CANCER THERAPY™

- Tumor Size
- Hypervascularity
- Inflammation
- Stress
- Anxiety
- Tumor Markers
- Angiogenesis

- Energy
- Mobility
- Strength
- Quality of Life
- Gut Health
- Liver Function

Immune Response

Appetite

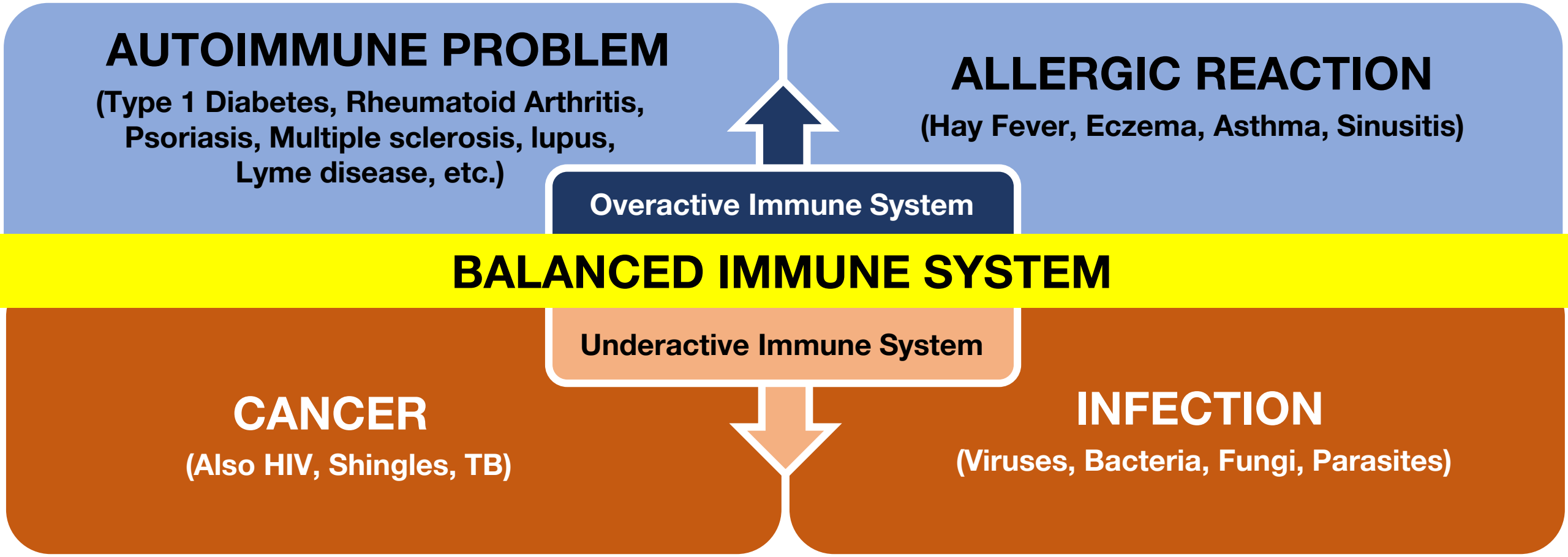
Emotions

Hormone Balance

THE SEVEN KEY PRINCIPLES OF CANCER THERAPY™

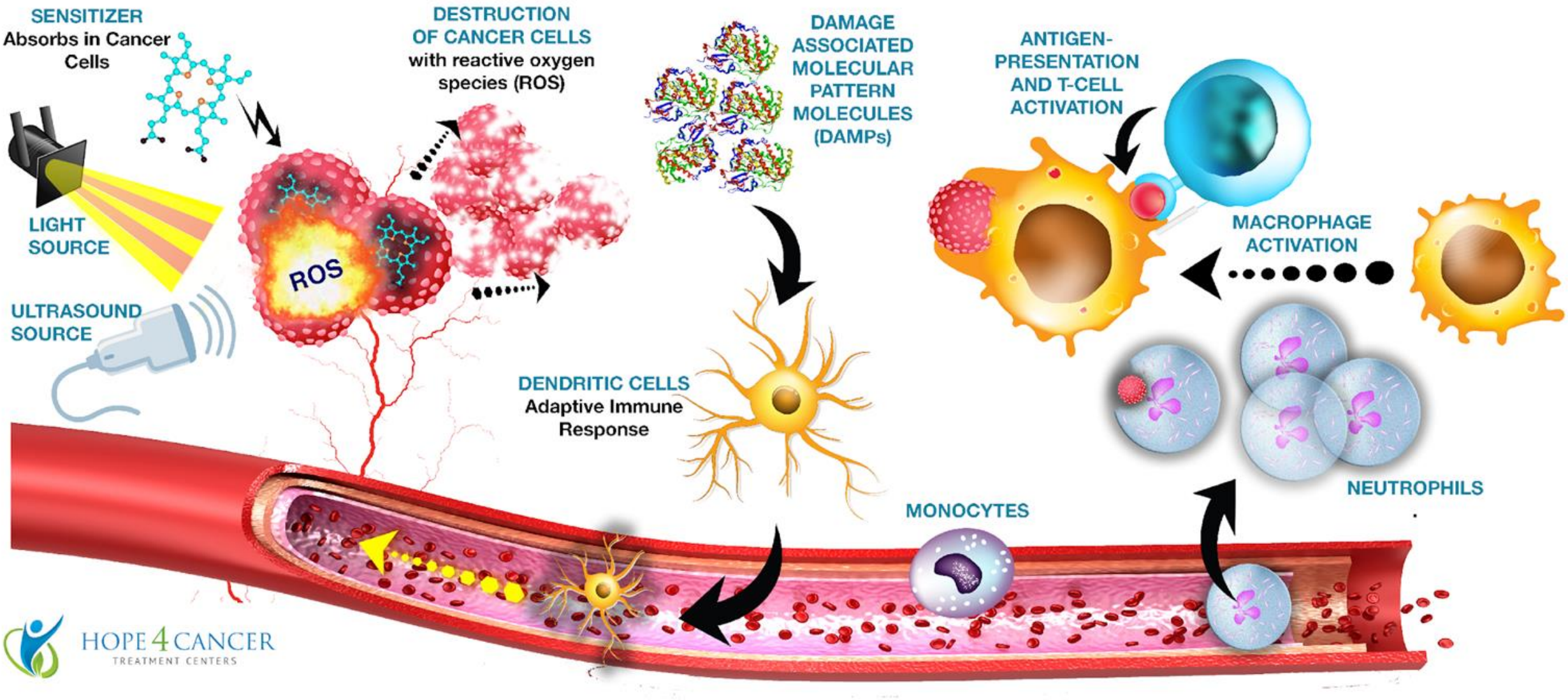
Non-Toxic Therapies That Impact the Immune System

IMMUNOMODULATION



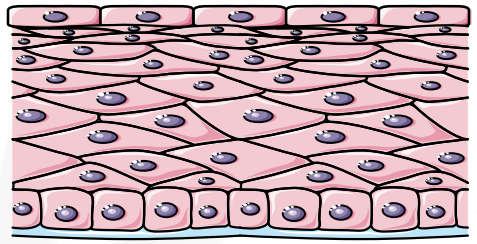
Source: Hope4Cancer Treatment Centers

SONO-PHOTO DYNAMIC THERAPY

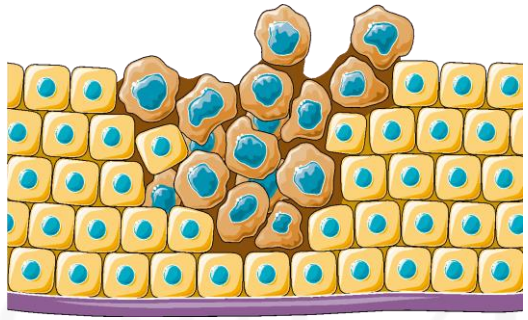


Source : Hope4Cancer Treatment Centers

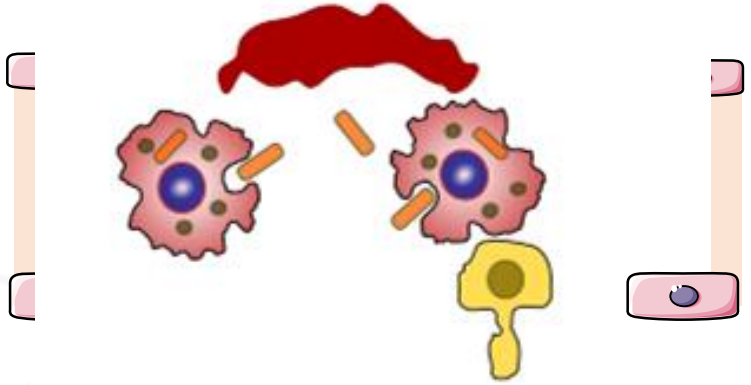
SONO-PHOTO DYNAMIC THERAPY



ENDOTHELIAL CELLS



TUMOR CELLS



MICROVASCULAR SHUTDOWN

TUMOR HYPOXIA

ORGANELLE DAMAGE

APOPTOSIS / NECROSIS

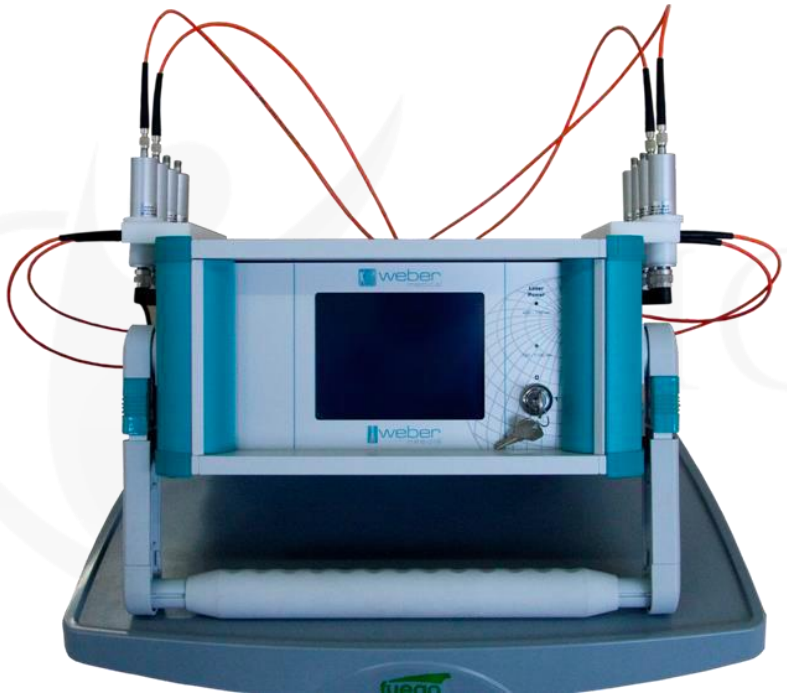
INNATE IMMUNITY

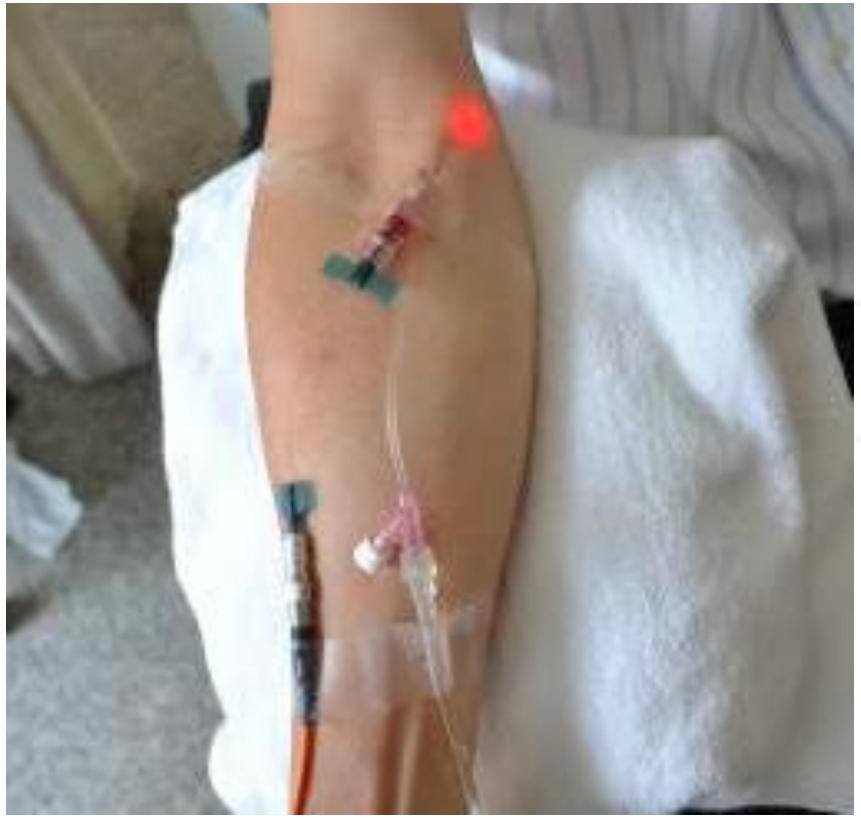
ADAPTIVE IMMUNITY

TUMOR ERADICATION

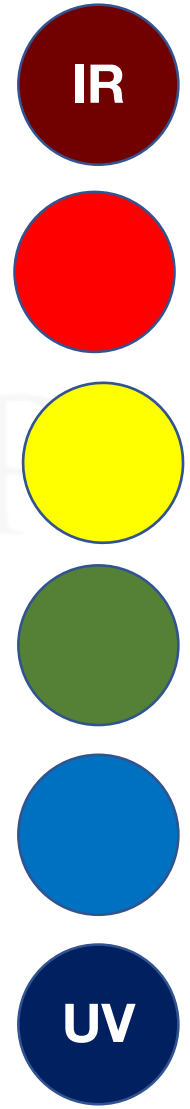
Image Source: Hope4Cancer Treatment Centers; Adapted from: Weber, M.H. (2017) Presentation at 12th International ISLA Congress, Lauenfoerde, Germany.

USE OF LASERS IN PHOTODYNAMIC THERAPY





LASERS



- Approved by FDA in the United States for external applications (off-label use for IV applications)
- CE Approved (Europe)

INTERSTITIAL PDT LASER APPLICATION

Source: Hope4Cancer Treatment Centers, Baja California

GcMAF TIMELINE

SAISEI-MIRAI PUBLICATIONS

1992
Dr. Yamamoto meets Dr. Hori at Tokushima University and GcMAF research starts at T.U.

YAMAMOTO PUBLICATIONS

2011
Second Generation GcMAF (injectable) developed at Saisei-Mirai, start of clinical use

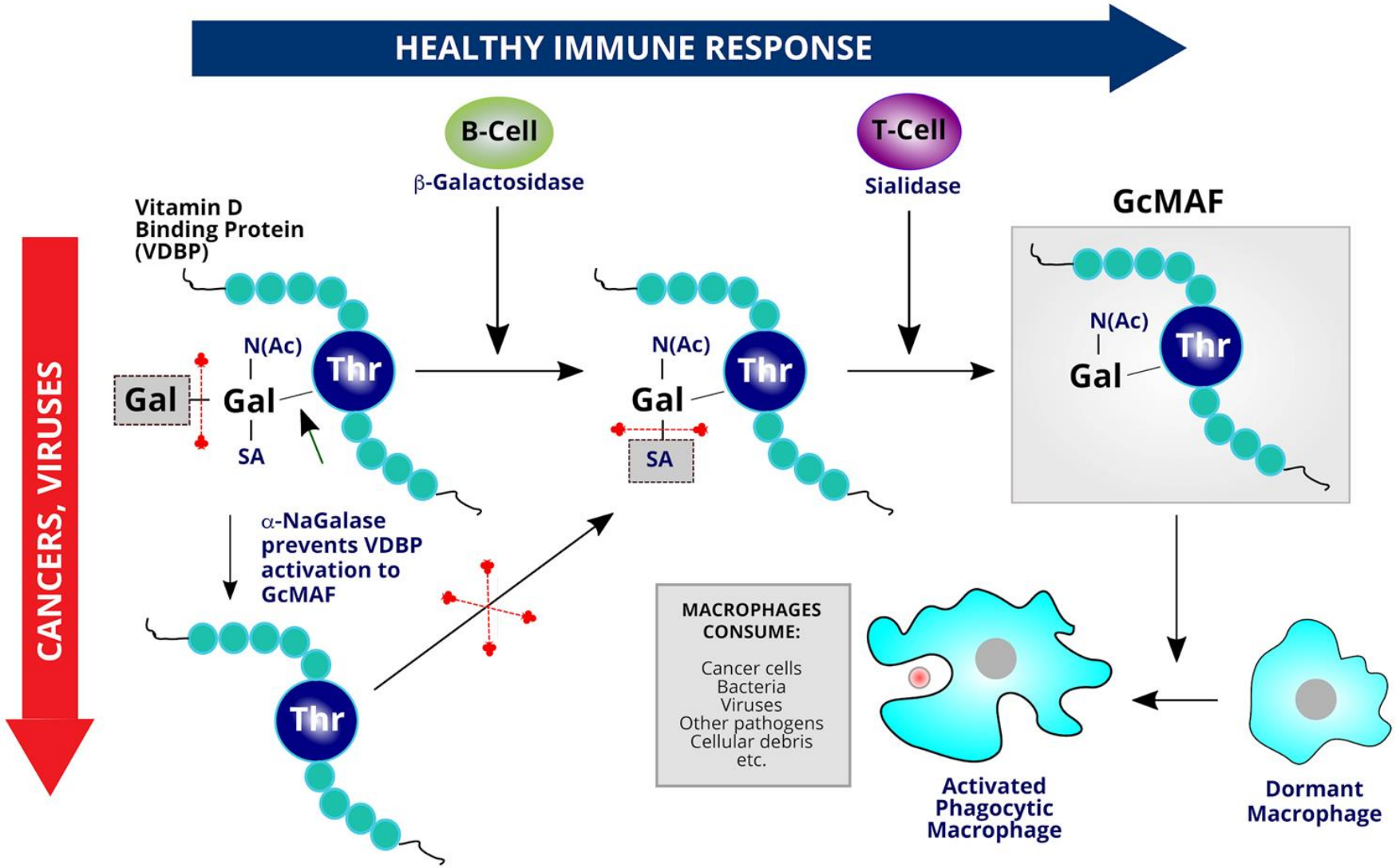
2016
Fourth Generation GcMAF (Recombinant) developed at Saisei-Mirai

1991
Dr. Yamamoto develops GcMAF and discusses Nagalase hypothesis

2010
Tokushima University begins collaboration with Saisei-Mirai

2014
Development of Third Generation GcMAF: oral Colustrum MAF at Saisei-Mirai

GcMAF: MECHANISM OF ACTION HYPOTHESIS



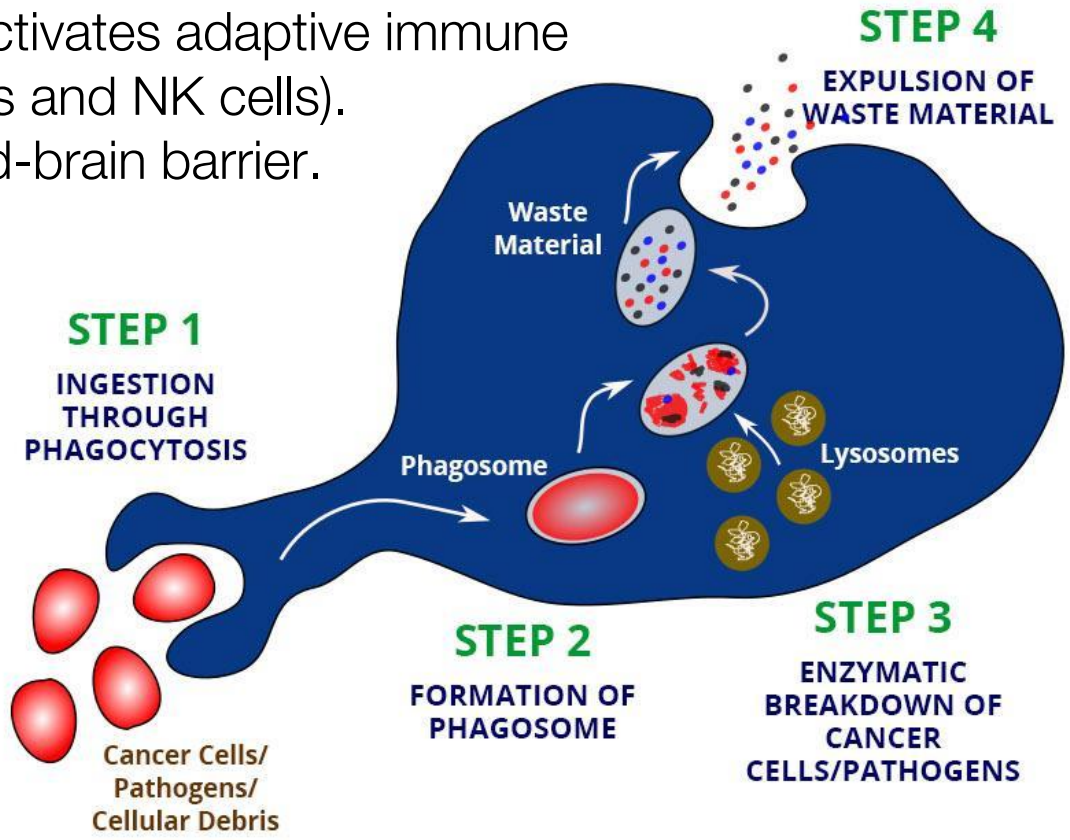
Current understanding of the complexity of macrophage subtypes and the tumor microenvironment suggests that the nagalase hypothesis provides only a limited view of how GcMAF actually works in the body.

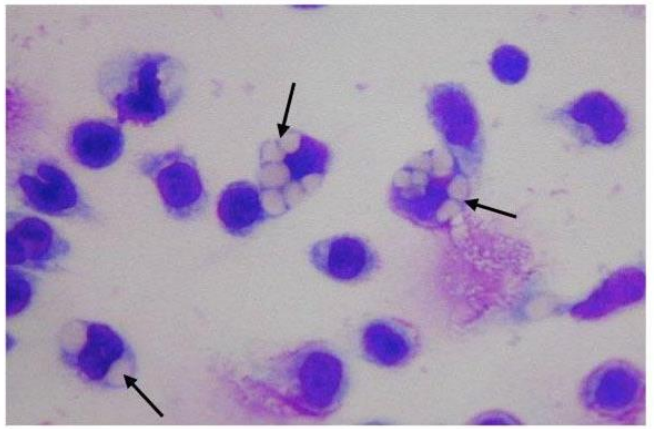
What is known are the effects of GcMAF in the immune system based on cellular level studies and clinical experience.

Image Source: Hope4Cancer Treatment Centers. Adapted from: Yamamoto, N.; Kumashiro, R. *J. Immunol.* **1993,** *151* (5), 2794-2802.

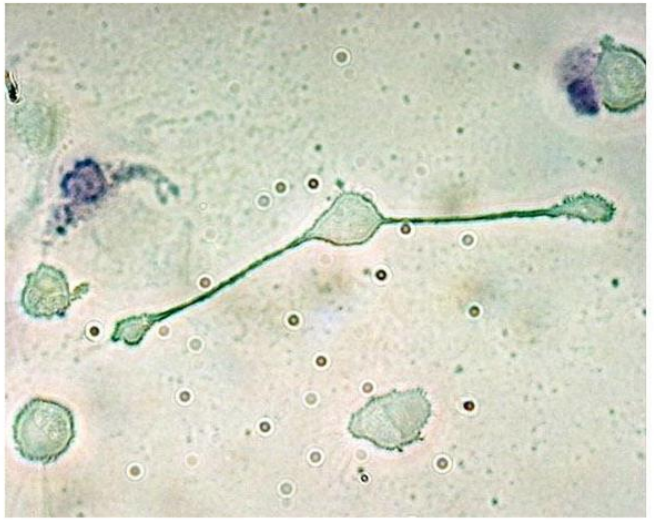
GcMAF: ACTIVATION OF MACROPHAGES

- Activates phagocytic macrophages in the tumor microenvironment
- Generates superoxide free radicals
- Increases rate of maturation of dendritic cells, which activates adaptive immune system (T cells and NK cells).
- Crosses blood-brain barrier.



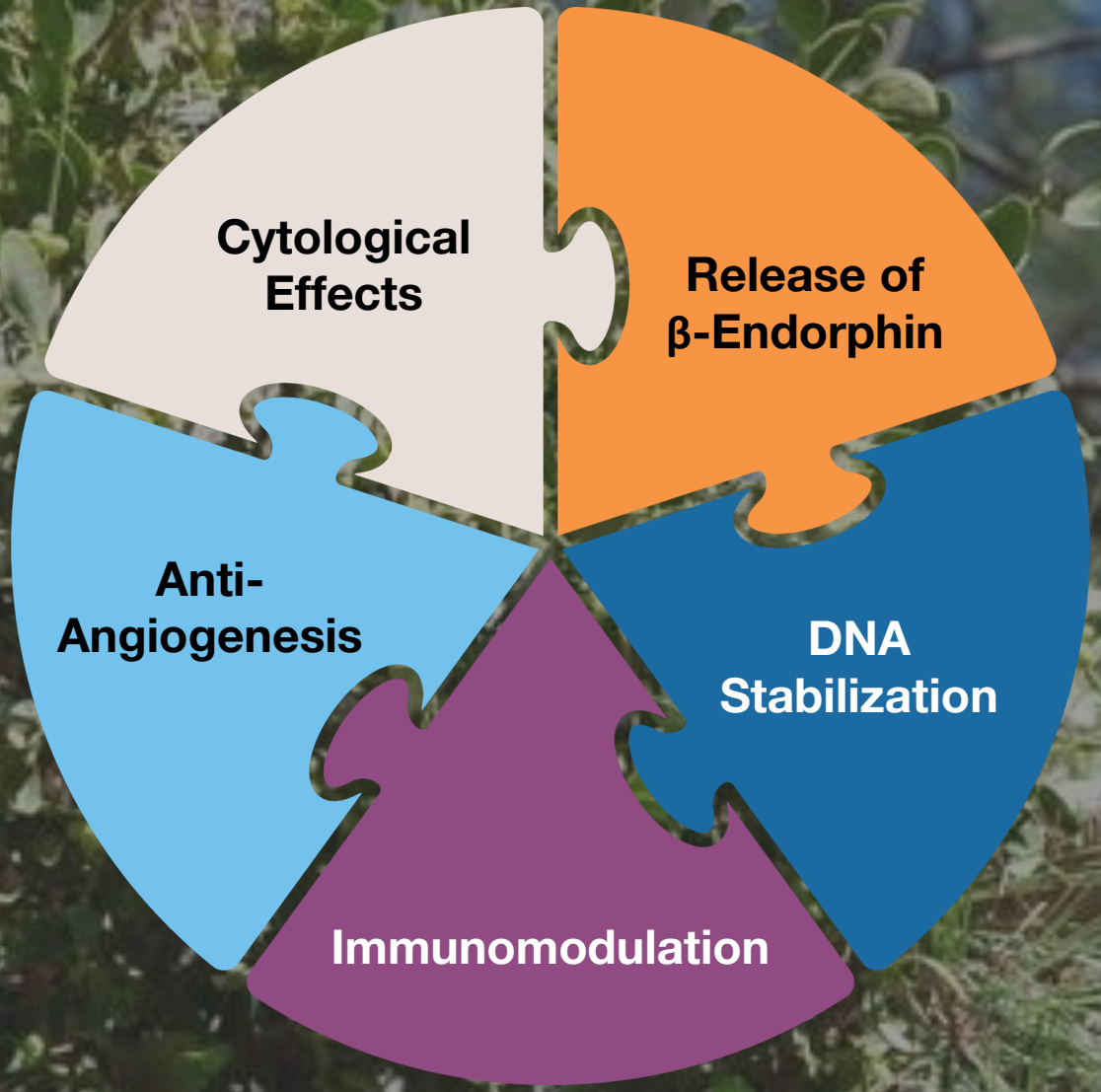


Phagocytosis assay with GcMAF shows cells being internalized by macrophages (courtesy: Saisei-Mirai, University of Tokushima))



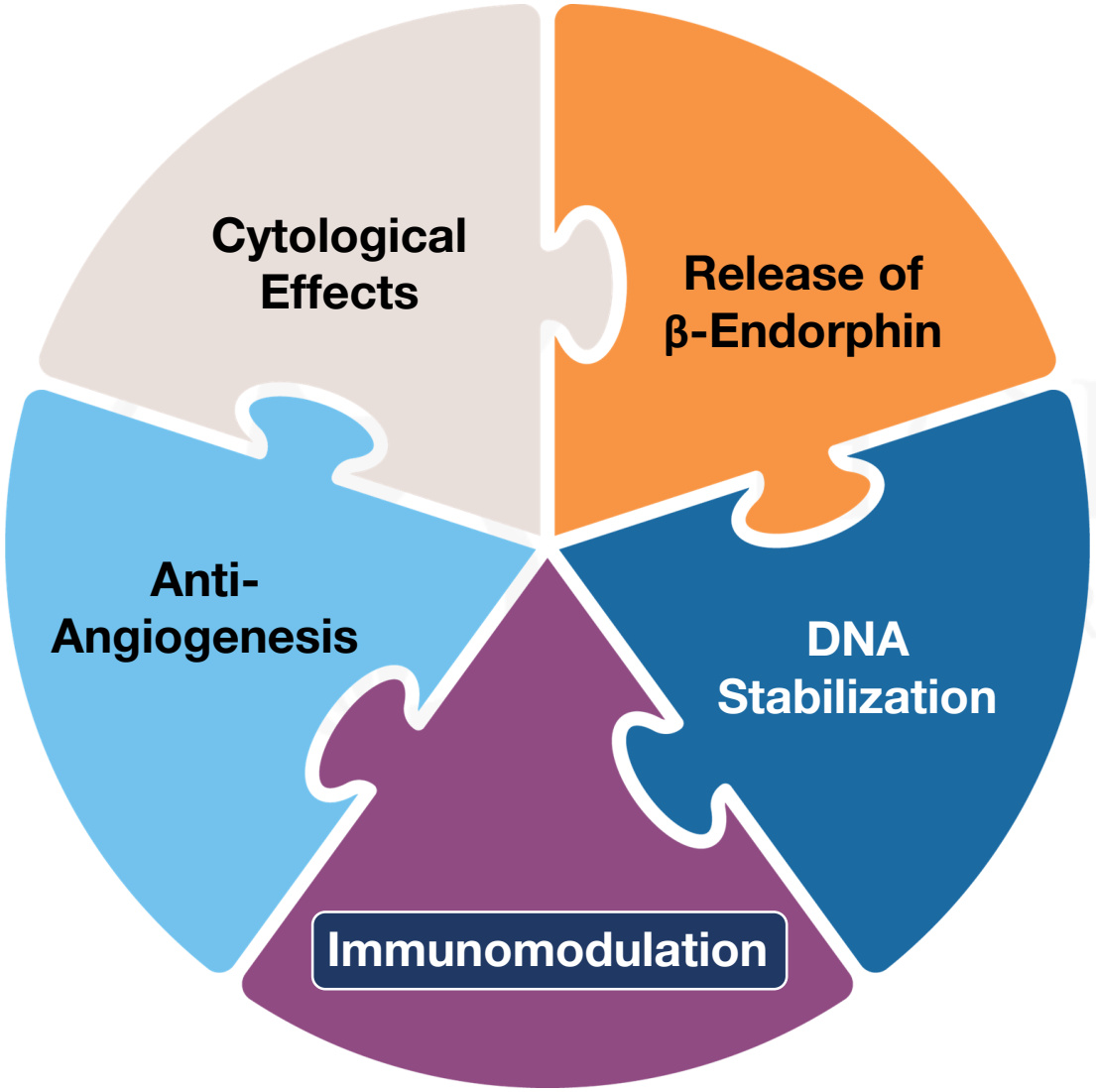
Macrophage spreading its pseudopods (arms) to entrap pathogens.

MISTLETOE THERAPY



Source: Helixor Handbook

MISTLETOE THERAPY



IMMUNOMODULATORY EFFECTS

Pharmacological Effects:

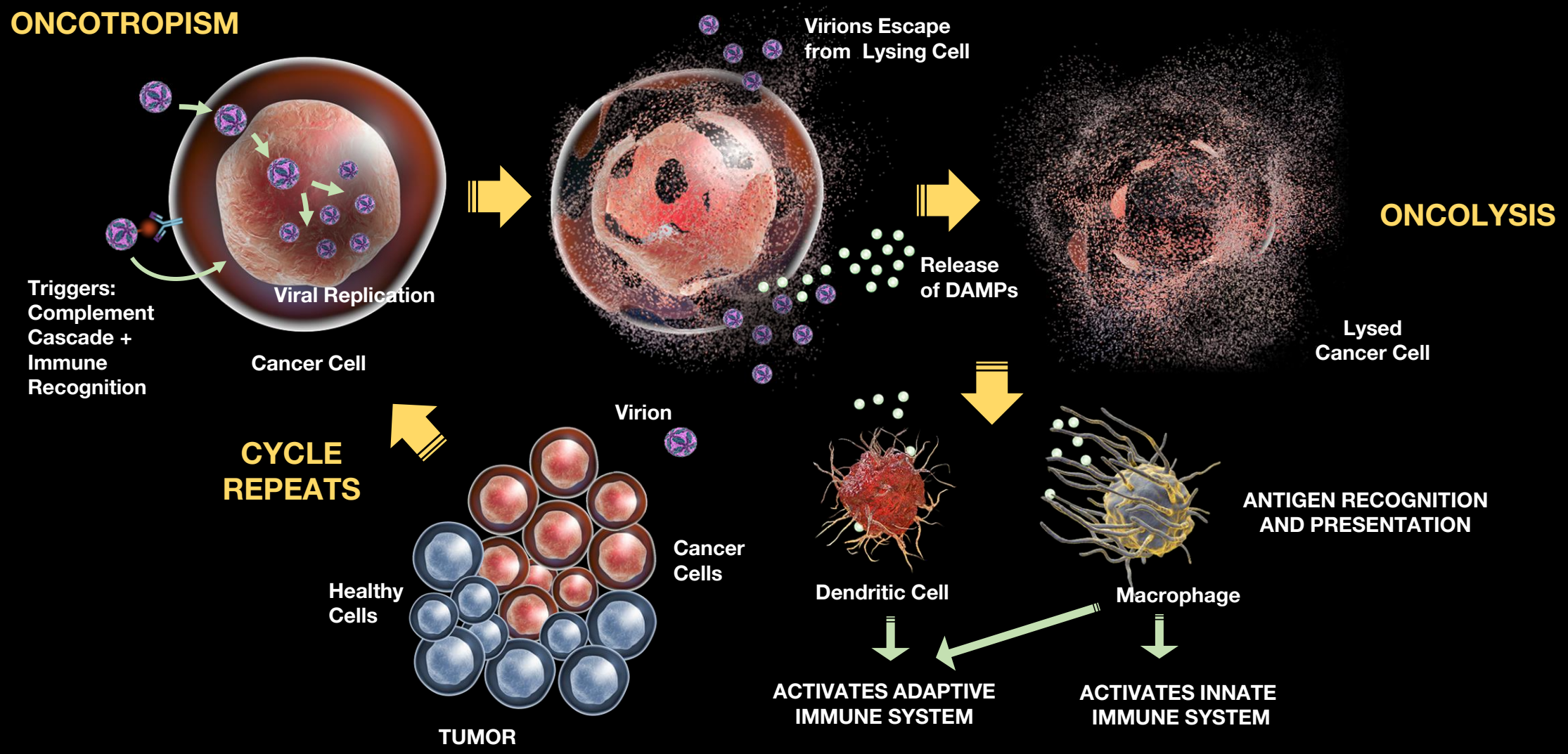
- Increased amount and activity of many types of immune cells (e.g. dendritic cells, B-cells, T-cells).
- Release of cytokine transmitters (e.g. IL-1, IL-6, TNF-α, IFN-γ, GM-CSF)

Clinical Relevance:

- Indirect immune-mediated tumor inhibition
- Lower susceptibility to infections (frequent cause of death of cancer patients)

Source: Helixor Handbook

ONCOLYTIC VIROTHERAPY



DAMPs = Damage Associated Molecular Pattern Molecules

ONCOLYTIC VIROTHERAPY

- Oncolytic Virotherapy is classified as an immunotherapeutic agent in Latvia because of its specific ability to cause immune-mediated damage to tumor cells.
- Oncolytic Virotherapy stimulates humoral immunity which includes B cells, antibody production, induction of interferon activity simultaneously with activation of cellular T-system immunity processes.
- In peripheral blood, cytotoxic CD38+, CD95+ and activated T cells are elevated along with apoptosis receptors.
- Thus, the repeated courses of Oncolytic Virotherapy taken by a patient are designed to encourage a sustained immune system response that, in the long term, favors tumor rejection.
- It has been shown in clinical situations, that repeated application of Oncolytic Virotherapy results in the gradual regression of lymph node micrometastasis and subcutaneous metastasis in melanoma patients.

OTHER THERAPIES USED

The following additional therapies directly and indirectly assist the immune system :

- **Hyperthermia (Local and Full Body)**
- Autologous Antigen Receptor Specific Oncogenic Target Acquisition (AARSOTA)
- **Vitamin C IV Therapy**
- **Nutrition Therapy**
- **ATP-I**
- **Personalized Supplementation and Nutrients - including Vitamin D and Propolis**
- **Lymphatic Massages**
- **Hormonal Optimization**

TAKE HOME MESSAGES

- While “new age” immunotherapeutics present powerful new opportunities to treat cancer, success data remains limited with most patients remaining untreatable with the new methods.

- We believe that the reason for a lack of success is rooted more in the philosophical approach to patient therapy, rather than the treatments themselves. A change in approach is, therefore, essential.

- Artificially suppressing or activating immune pathways is not equivalent to restoring immune health – in fact, it can be the opposite, having seriously negative consequences.

- A proper immune therapeutic protocol is an essential part of any cancer therapy with the aim of strengthening the body’s intrinsic immune system.

- Reducing tumor load, improved oxygenation, and removal of toxins are essential aspects to consider while attempting to reboot the cancer patient’s immune system.

- The Seven Key Principles of Cancer Therapy were developed with the precise intentions to avoid toxicity and treat the whole body from a body-mind-spirit perspective – aspects which cannot be ignored as we converge into a brave new world of cancer therapies.