COVID-Cancer-HOPE

Connecting the Dots

Let's Start

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Connecting the Dots

Let's Start

Relevant Financial Disclosures

- Brio-Medical
  - Medical Director
  - Speaker
- NEO7BioScience
  - Medical Advisor Board Member
  - Speaker/Consultant

“Students today are educated collecting dots. Almost none of it spent teaching them the skills necessary to connect dots.”

— *Seth Godin*

“You can't connect the dots looking forward; you can only connect them looking backwards...”

—Steve Jobs

Objectives

- What is TurboCancer? Is it real?
- Connect the dots of Covid and Cancer
- Connect the dots of Long-Covid to cancer
- Is SARS-CoV-2 an OncoVirus?
- Connect the dots of Covid, Cancer, and Hope

“The Party told you to reject the evidence of your eyes and ears. It was their final, most essential command.

— George Orwell, 1984

“A hospital alone shows what war is.”


“A hospital alone shows what war is.”

Turbo-Cancer

Turbo (adjective)—(1900 origin) turbine, implies power, vector, and force

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“…reject the evidence of your eyes and ears…”

Turbo Cancer

COVID-19 and other underlying causes of cancer deaths—United States, January 2018–July 2022

The narrative spin cycle was seen in full force with an article published in the UK Daily Mail press which said that there was a **1.5%** decline in cancer deaths over the same time period (2019-2020).

From 2018 to 2021, the number of cancer deaths increased by 4.7%. To be more precise, the number of deaths with cancer as the primary underlying cause increased by 1.0% over the same time period.

“turbo-charging of chemotherapy”

“Turbocharging the T cell to fight cancer”

“race to supercharge cancer-fighting T cells”

Turbo Charge away!!!

American IS winning war on cancer: Death rates have fallen 33% since 1991 — averting 3.8MILLION deaths

- **Over the last three decades fatalities have declined by 33% from all cancers**
- **Dropping rates of lung and breast cancer mortality were behind it**
- **Joe Biden is aiming to halve cancer deaths over the next 25 years**

By LUKE ANDREWS HEALTH REPORTER FOR DAILYMAIL.COM
PUBLISHED: 17:28 EST, 12 January 2023 | **UPDATED:** 18:15 EST, 12 January 2023

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The **cancer** death rate in the US has plummeted 33 percent in the past three decades, according to reassuring data highlighting the country's progress in fighting

“…reject the evidence of your eyes and ears…”

Turbo Cancer

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“race to supercharge cancer-fighting T cells”

Turbo Charge away!!!

COVID-19 and Other Underlying Causes of Cancer Deaths — United States, January 2018–July 2022

Weekly / December 16, 2022 / 71(50);1583–1588

S. Jane Henley, MSPH[1]; Nicole F. Dowling, PhD[1]; Farida B. Ahmad, MPH[2]; Taylor D. Ellington, MPH[1,3]; Manxia Wu, MD[1]; Lisa C. Richardson, MD[1] (VIEW AUTHOR AFFILIATIONS)

View suggested citation

Summary

What is already known about this topic?

Persons with cancer are at increased risk for dying from COVID-19.

What is added by this report?

Among persons who died with cancer, 2.0% in 2020 and 2.4% in 2021 had COVID-19 listed as the underlying cause of death, with higher percentages during COVID-19 peaks and among persons who were older, male, Hispanic or Latino, non-Hispanic American Indian or Alaska Native, non-Hispanic Black or African American, or living with leukemia, lymphoma, or myeloma.

What are the implications for public health practice?

These results might guide COVID-19 prevention interventions and efforts focusing on reducing health disparities and addressing structural and social determinants of health among cancer survivors, which might help protect those at disproportionately increased risk for dying from COVID-19.

Article Metrics

Altmetric: 15 Twitter (27) Facebook (1)

Citations:

Views:
Views equals page views plus PDF downloads

Metric Details

Figures

Figure 1

Ute Krüger, MD, DMedSci

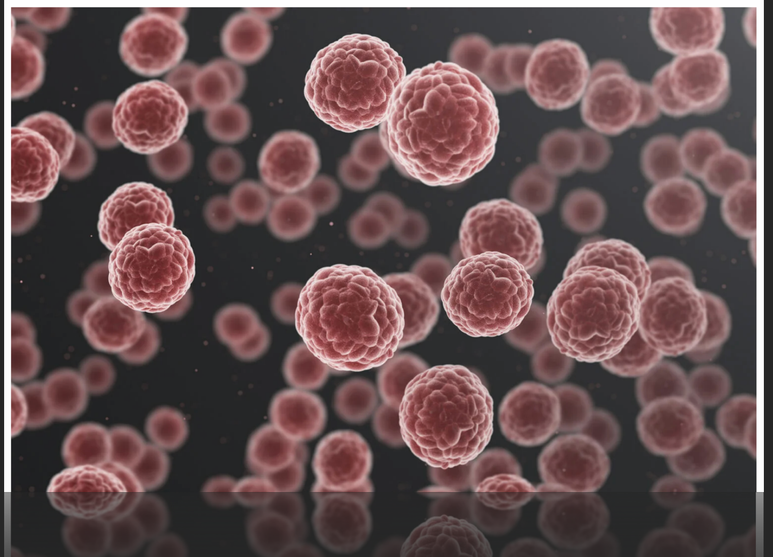
"But now it feels like I'm watching people being killed and I cannot do anything. As a pathologist, I diagnose tumors that maybe have been caused by another colleague with a shot."

"We found that this risk is increasing with each generation."

– Shuji Ogino, professor, physician-scientist

HEALTH & MEDICINE

Dramatic rise in cancer in people under 50

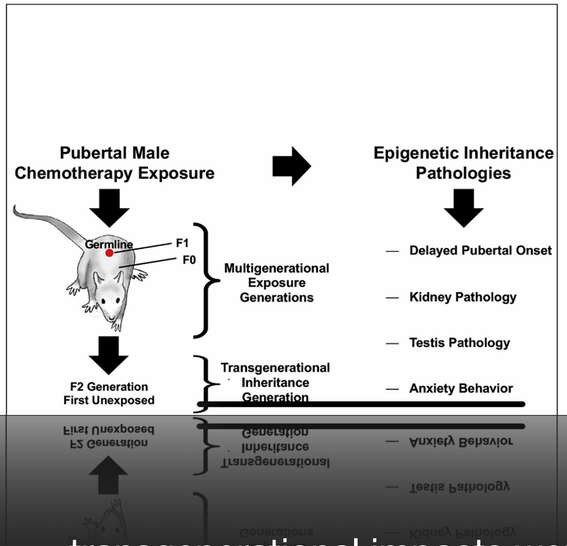


iScience

CellPress
OPEN ACCESS

Article

Examination of generational impacts of adolescent chemotherapy: Ifosfamide and potential for epigenetic transgenerational inheritance



Ryan P. Thompson, Daniel Beck, Eric Nilsson, Millissia Ben Maamar, Margarett Shnorhavorian, Michael K. Skinner

skinner@wsu.edu

Highlights

Chemotherapy-induced sperm DNA methylation facilitates epigenetic inheritance

Chemotherapy promotes epigenetic transgenerational inheritance of pathology

Pubertal exposure to chemotherapy impacts later life sperm

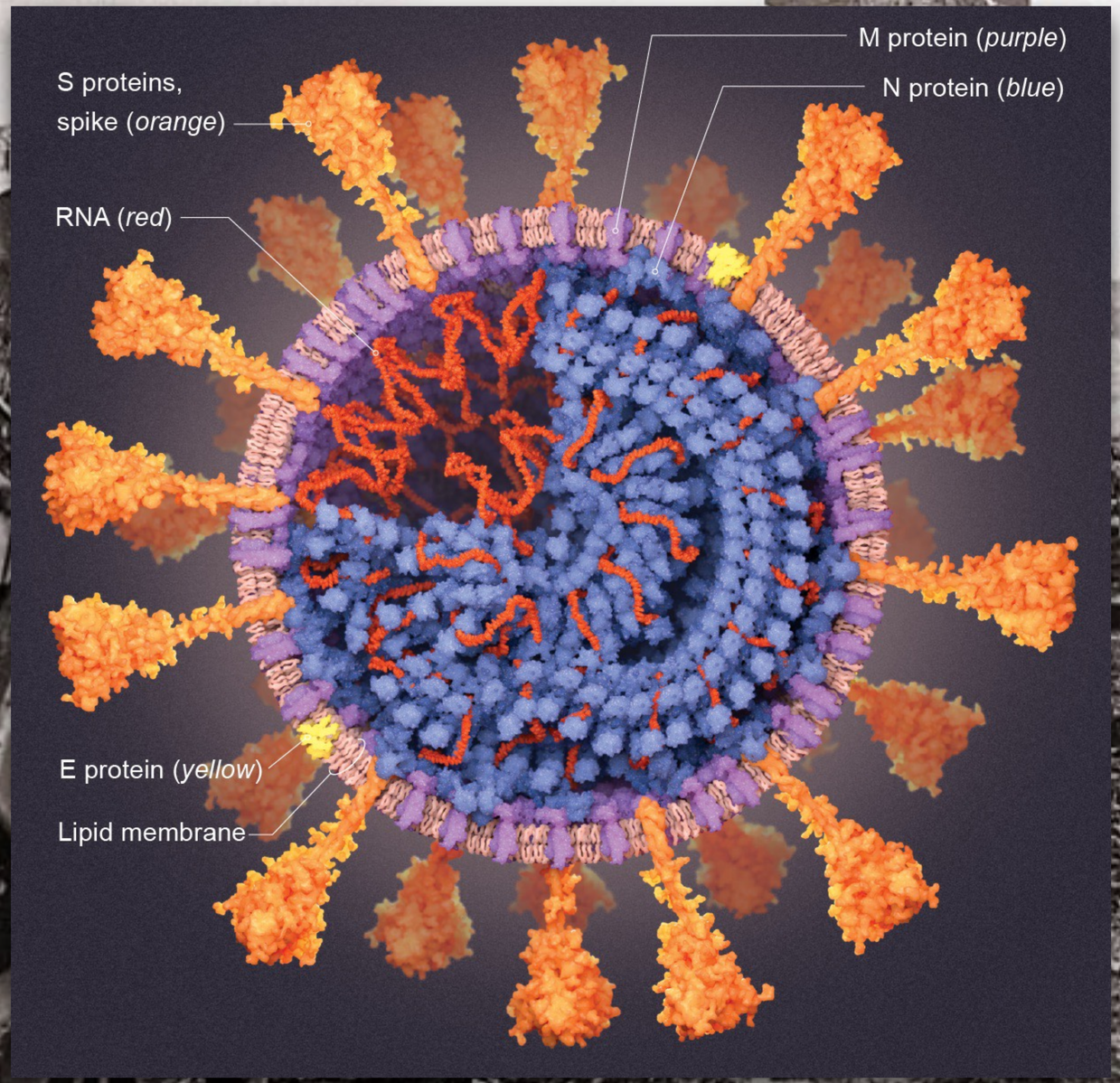
transgenerational impacts were the most prominent in the **<u>fourth and sixth generations</u>**

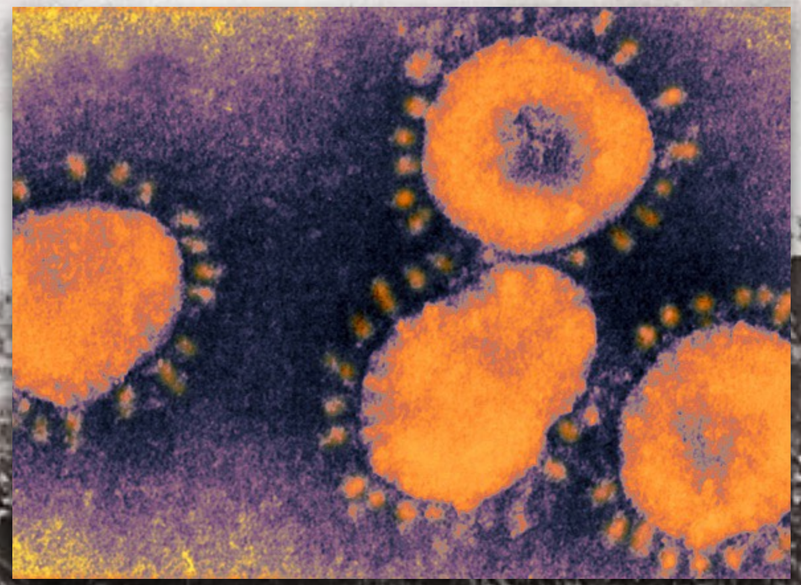
- hot
- blistering
- hypersonic
- supersonic
- meteoric
- lightening
- breakneck
- whirlwind
- fast
- speedy
- fast-tracked
- zippy

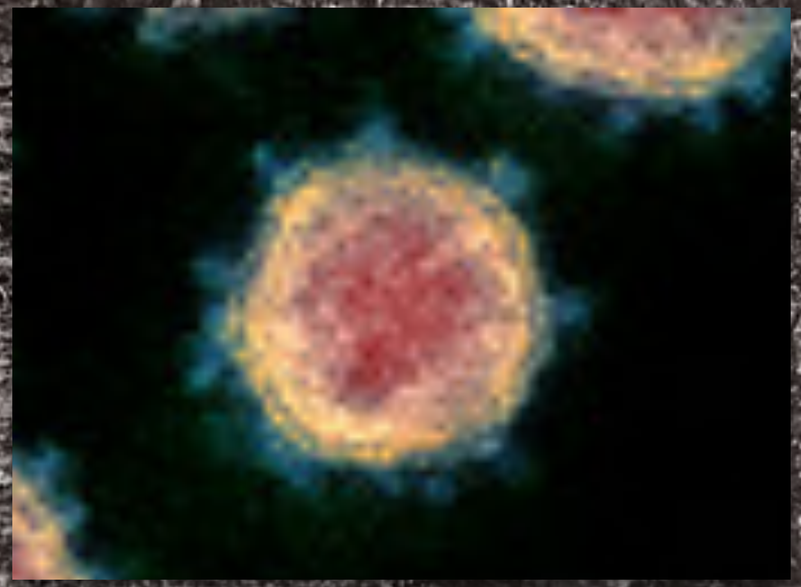
Synonyms

“a word or phrase that means exactly or nearly the same as another word or phrase”


The board is
Set
“The blunders are all there on the board, waiting to be made.”
– Savielly Tartakower


S proteins,
spike (*orange*)
RNA (*red*)
E protein (*yellow*)
Lipid membrane
M protein (*purple*)
N protein (*blue*)

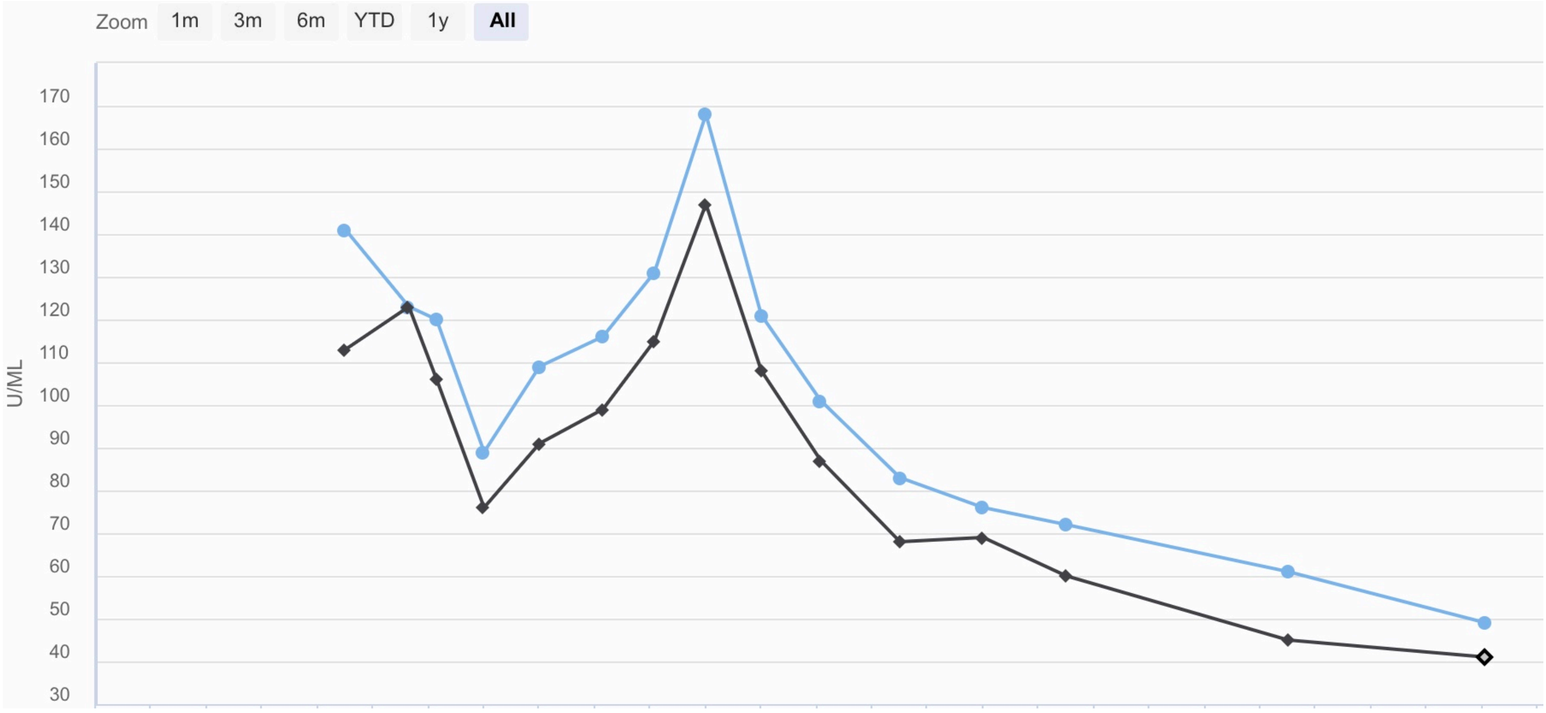




KB

Case study #1

- Stage IV ER+/PR+/HER-2- recurrent breast cancer
- Diagnosed in 2010
- Treatment initiated in 2019
- No Evidence of Disease
- COVID infection December, 2021
- Then…



Breast cancer biomarkers

KB

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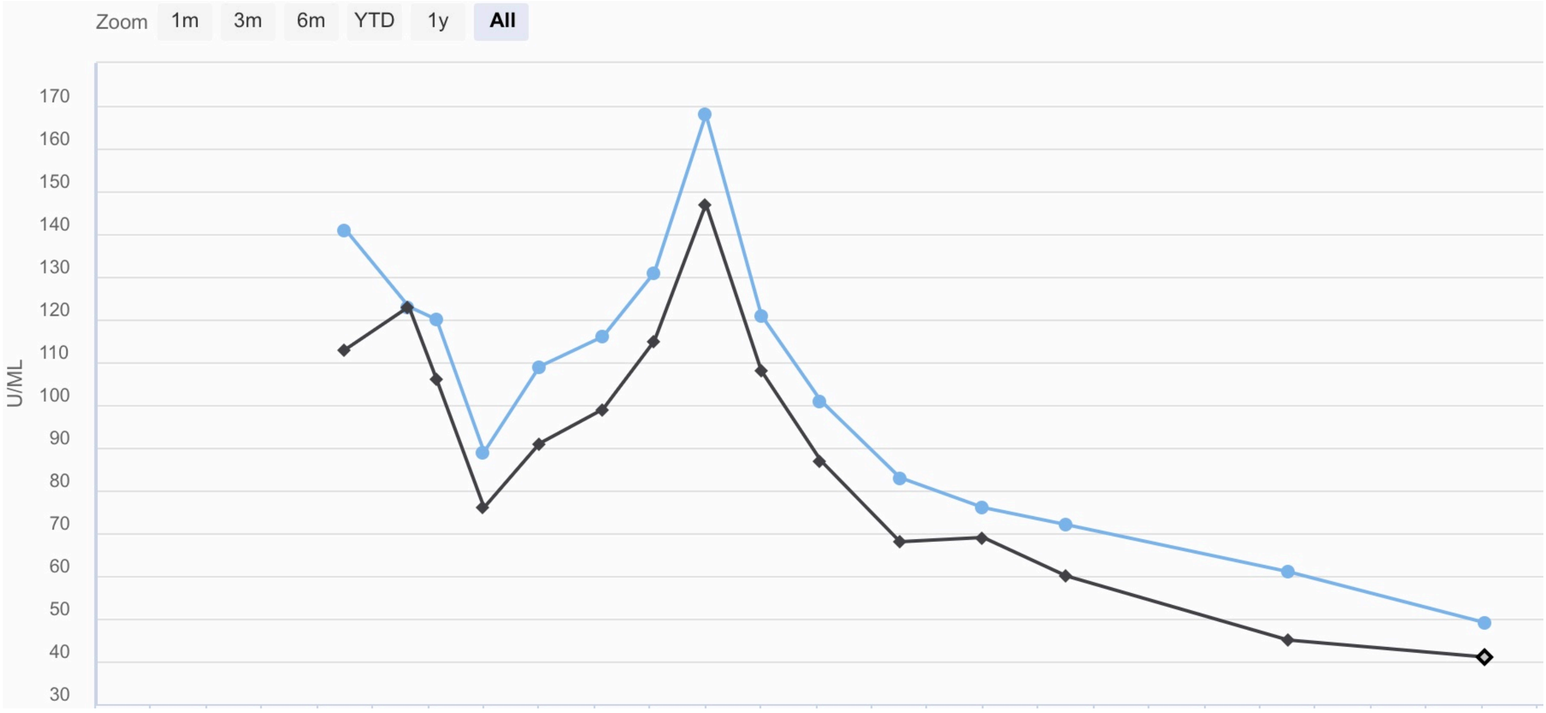


Breast cancer biomarkers

"Without a doubt, the ability to connect the dots is rare, prized and valuable. Connecting dots, solving the problem that hasn't been solved before, seeing the pattern before it is made obvious, is more essential than ever before. Why then, do we spend so much time collecting dots instead? More facts, more tests, more need for data, even when we have no clue (and no practice) in doing anything with it. Their big bag of dots isn't worth nearly as much as your handful of insight, is it?"

— Seth Godin

“An asteroid or a supervolcano could certainly destroy us, but we also face risks the dinosaurs never saw: An engineered virus, nuclear war, inadvertent creation of a micro black hole, or some as-yet-unknown technology could spell the end of us.”

—Elon Musk

September 30, 2008

—Elon Musk

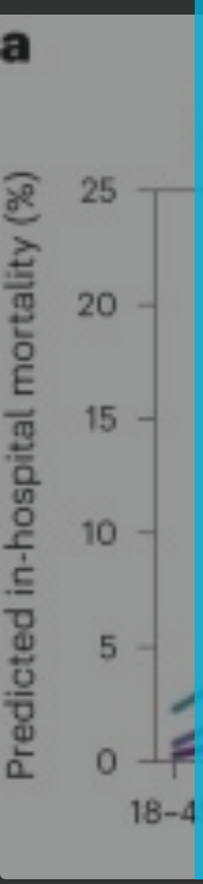
Spike protein disease

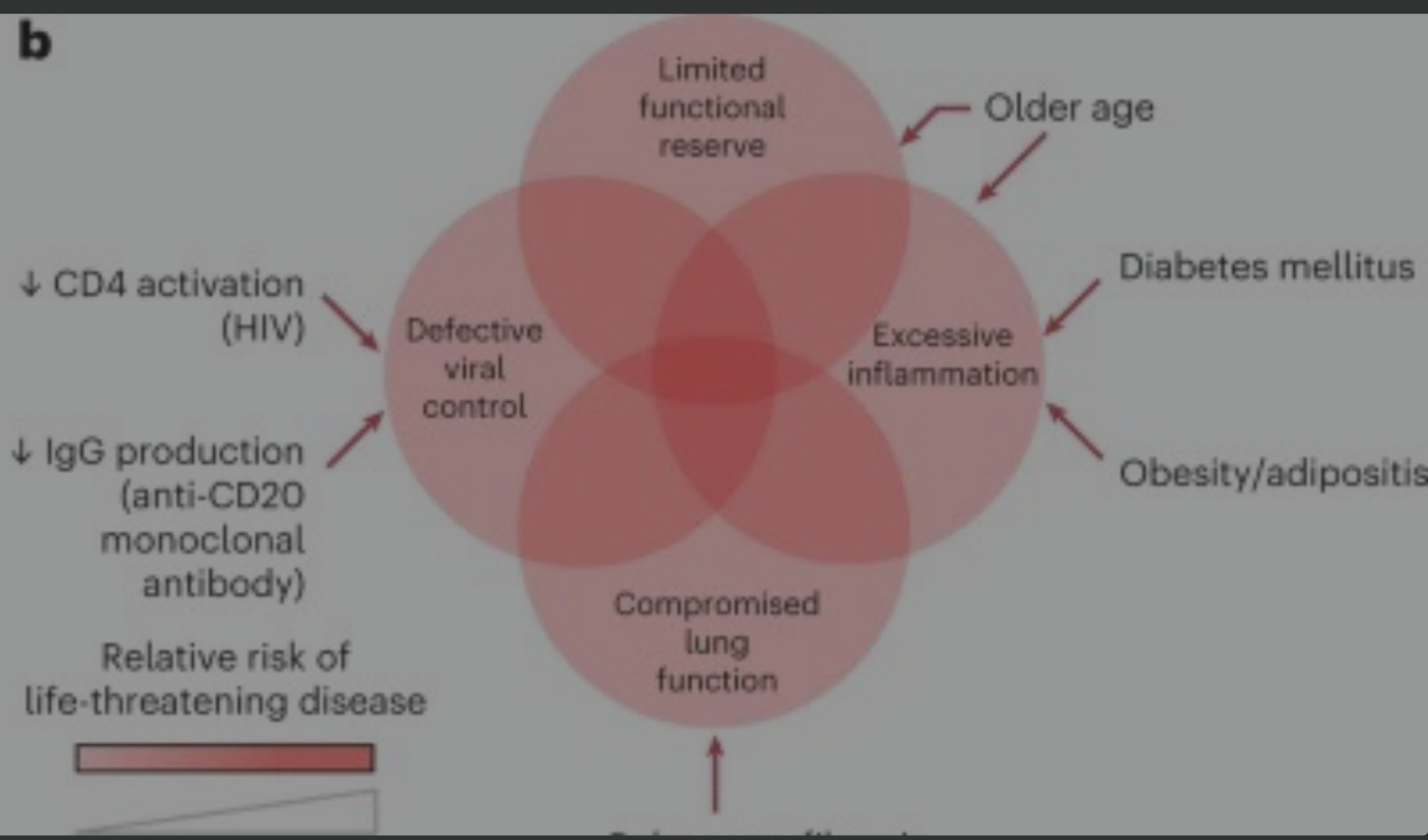
Whether by injection or infection

- Comorbidities
- Toxins
- Receptors
- Lipopolysaccharide (LPS)
- NF-κB signaling
- Platelets
- Circulating Tumor Cells (CTC)
- Immune effects
- Metastasis

Comorbidities

“Here, we use the term ‘**comorbidity**’ to refer to any long-term health condition that coexists in an individual with a specific condition of interest, in this case COVID-19. This is distinct from **multimorbidity**, which describes the presence of two or more long-term health conditions in an individual without reference to COVID-19—and it is in itself a major, growing public-health challenge. Modeling studies have estimated that **1.7 billion people** globally (**22%** of the population) have at least one comorbidity that is associated with an increased risk of developing severe COVID-19.” (From *Russell CD, Lone NI. Baillie JK. Comorbidities, multimorbidity and COVID-19.*)

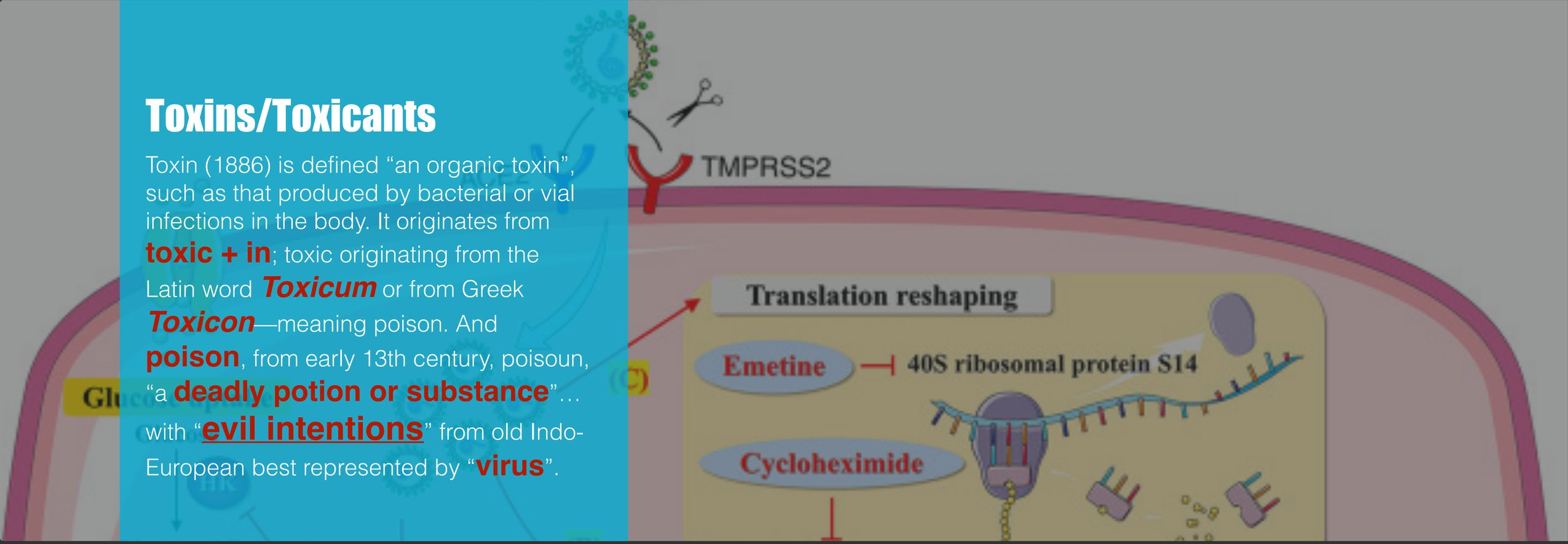




Cancer is listed as one of the many comorbidities, along with **male > female, obesity, advanced age, diabetes, hypertension, and cardiovascular disease**, in the SARS-CoV-2 increased infection risk profile. But, does listing cancer as a comorbidity mean that the spike protein, whatever the source, is the right approach to help people with cancer? That is a big question that I will work to answer by connecting a few dots. It is evident that the symptoms of long Covid follow the the pre-existing trail of chronic inflammation, immune disruption, and organ system disruption. It appears that long Covid merely **exacerbates that which pre-existed.**

Toxins/Toxicants

Toxin (1886) is defined “an organic toxin”, such as that produced by bacterial or vial infections in the body. It originates from **toxic + in**; toxic originating from the Latin word ***Toxicum*** or from Greek ***Toxicon***—meaning poison. And **poison**, from early 13th century, poisoun, “a **deadly potion or substance**”… with “**evil intentions**” from old Indo-European best represented by “**virus**”.

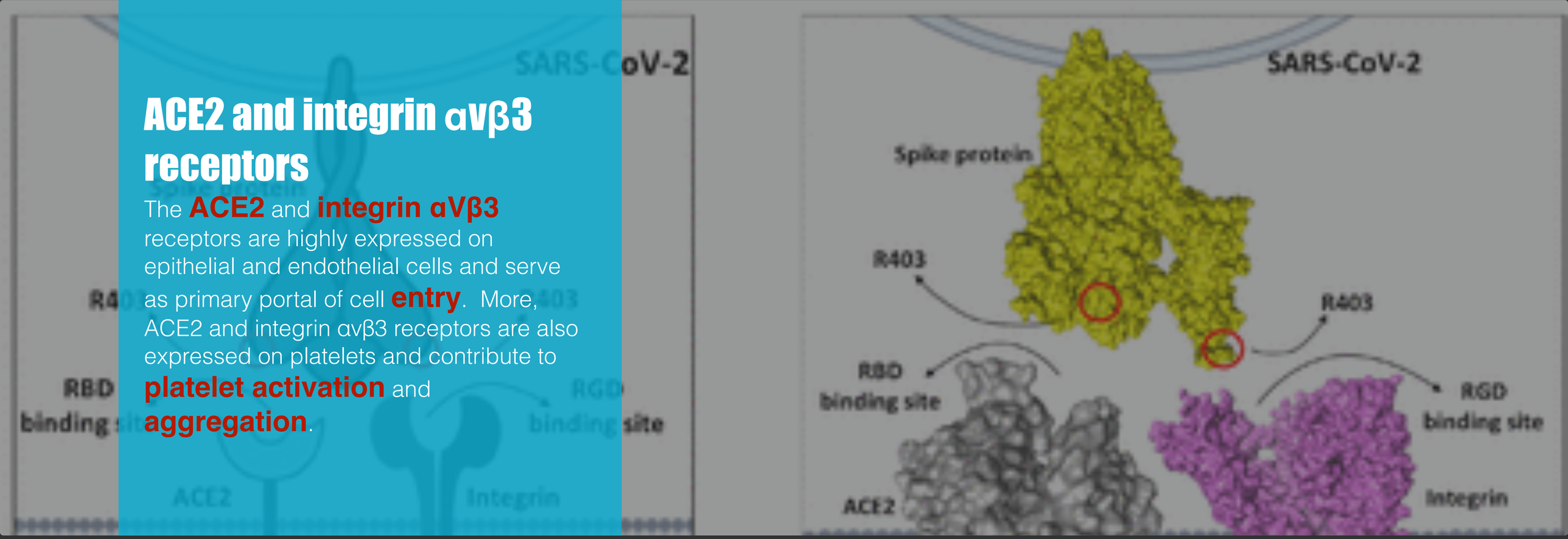


“SARS-CoV-2 may affect **tumor progression** through **multiple mechanisms**, including glycolysis, translational modification, nucleic acid synthesis, lipid metabolism and transcriptional splicing…The correlation of dynamic changes of COVID-19 antibody, nucleic acids, tumor metabolism pathway switch and levels of tumor-related cytokines with the prognosis during the disease course of patients with cancer is worthy of further study. Given SARS-CoV-2-activated…

toxic inhibitory effect on NK cells…” (from *Li YS, Ren HC, Cao JH. Correlation of SARS-CoV-2 to cancer: Carcinogenic or anticancer?*)

ACE2 and integrin αvβ3 receptors

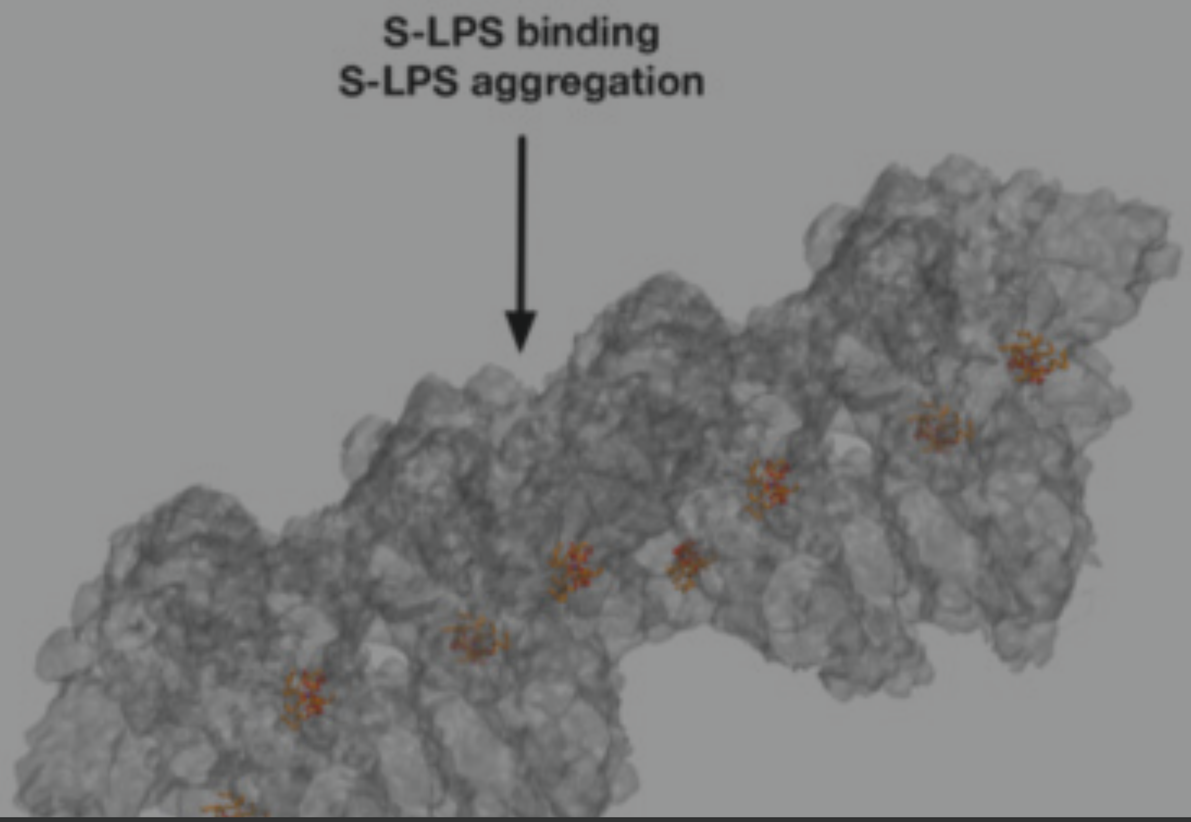
The **ACE2** and **integrin αVβ3** receptors are highly expressed on epithelial and endothelial cells and serve as primary portal of cell **entry**. More, ACE2 and integrin αvβ3 receptors are also expressed on platelets and contribute to **platelet activation** and **aggregation**.



SARS-CoV-2 **spike proteins** alone are shown to increase **platelet hyperactivity and platelet aggregation** via ACE2 and integrin αvβ3 receptors independently. The result is an increase in 1) **angiogenesis**, 2) **platelet–cancer cell aggregate formation**, 3) **CTC survival**, 4) **cultivation and preparation of pre-metastatic niche**, 5) **promotion of the tumor microenvironment**, 6) **micrometastasis**, and 7) ultimately **macrometastasis**. New dual-receptor mechanism between integrins and ACE2 receptors and the SARS-CoV-2 spike protein is shown to mediate **enhanced tissue tropism** If cancer metastasizes or spreads from its original site, certain cancers have a preference for certain organs. This is known as "**organ tropism**." (from *Nader D, Gressett TE, Hossen Md Lokeman. A dual-receptor mechanism between integrins and ACE2 widens SARS-CoV-2 tissue tropism.*)

Lipopolysaccharide (LPS)

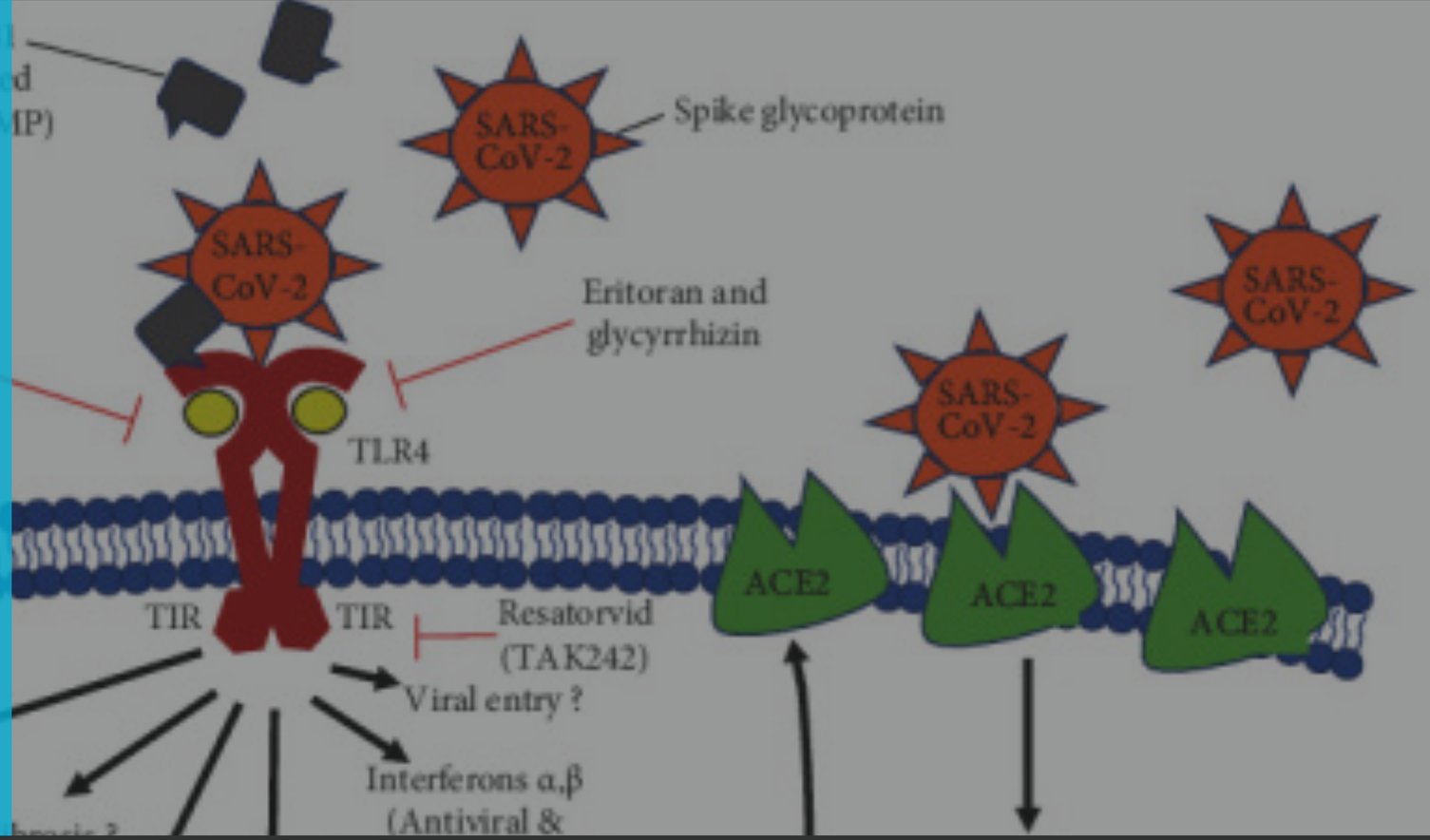
“LPS is the main component of the outer membrane of **Gram-negative bacteria** and is a well characterized **pathogen-associated molecular pattern (PAMP)** recognised by TLR4 in complex…LPS transfer through this series of proteins is a potent **trigger** of the inflammatory response in sepsis”



”Here, we demonstrate a previously unknown **interaction** between SARS-CoV-2 S protein and LPS, leading to a **boosting of proinflammatory actions** *in vitro* as well as *in vivo*. These results on the **synergism between LPS and S protein** have clinical and therapeutic importance, as this could give new insights in the comorbidities that may increase the risk for severe COVID-19 disease… its **pathogenetic** steps…” (from *Petruk G, Puthia M, Petrlova J et al. SARS-CoV-2 spike protein binds to bacterial lipopolysaccharide and boosts proinflammatory activity)*

Toll-Like 4 Receptors (TLR4)

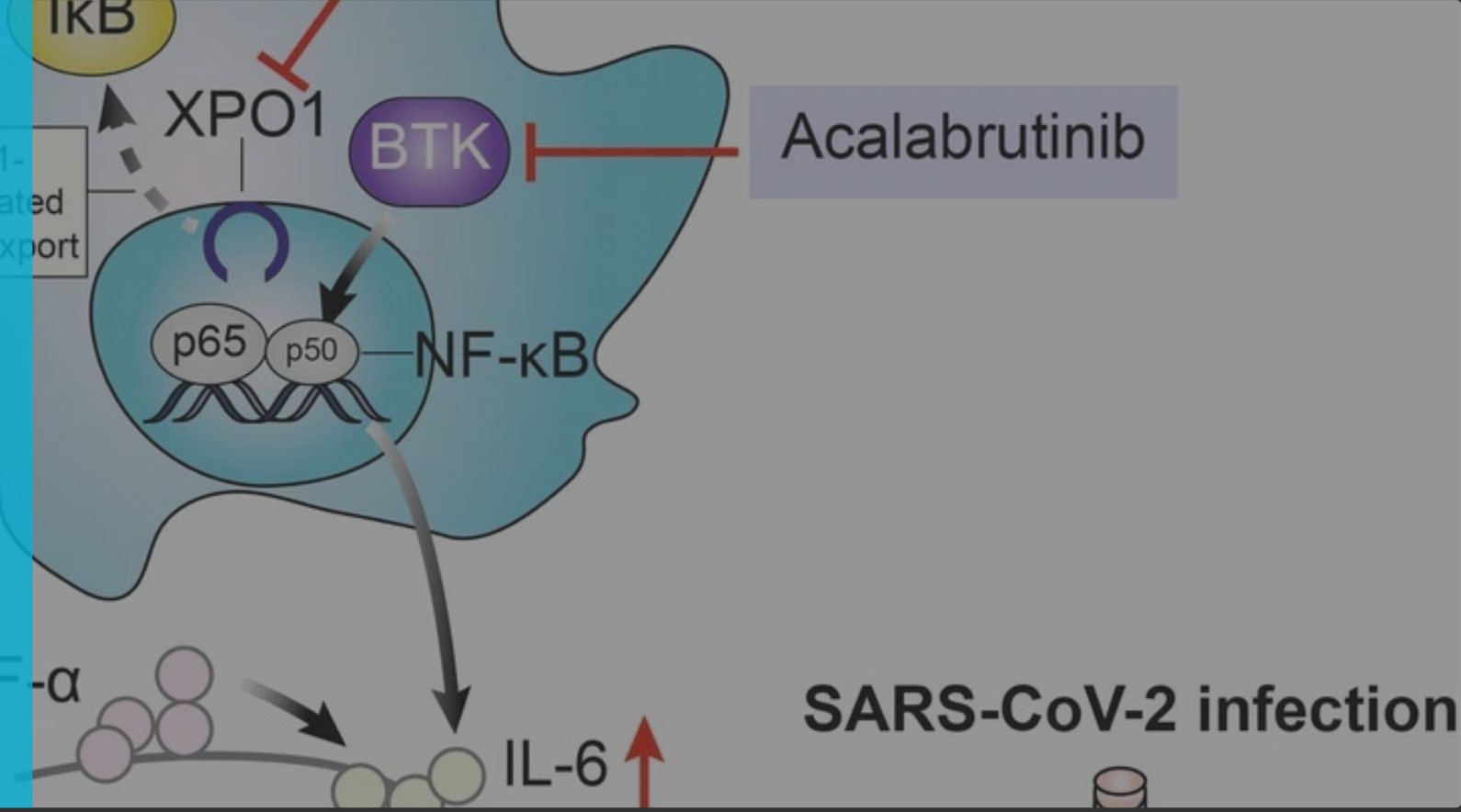
"**Increased expression and activity** of toll-like receptor 4 (TLR4) in chronic infectious and inflammatory conditions is **related** with **cancer progression**: its activation induces an inflammatory signaling that increases the **tumorigenic potential** of cancer cells promoting their **immune evasion**…activation of TLR4 supports tumor progression by stimulating the release of more effective immunosuppressive exosomes, which allow tumor cells to escape immune surveillance and probably even play a role in the **metastatic process**."



The SARS-CoV-2 viral **spike protein** has been shown to **stimulate** TLR4 receptors. Toll-like receptor 4 (TLR4) belongs to the family of **PATTERN RECOGNITION RECEPTORS (PRRs)**.The same TLR4 receptors are the means by which LPS will stimulate the chronic inflammation found in metabolic endotoxemia, diabetes, metabolic syndrome, cardiovascular disease, and **pro-cancer signaling**. According to a study published in August 2021, in the *International Journal of Molecular Sciences*, spike proteins from the SARS-CoV-2 virus will stimulate the same LPS mediated TLR4 receptor to increased inflammatory signaling via activation of NF-κB signaling. More important, the **two synergistically increase inflammatory signaling up to 50% above that of LPS or spike protein alone.** (from *Domenis R, Cifù A, Marinò D et al.Toll-like Receptor-4 Activation Boosts the Immunosuppressive Properties of Tumor Cells-derived Exosomes.*)

NF-κB signaling

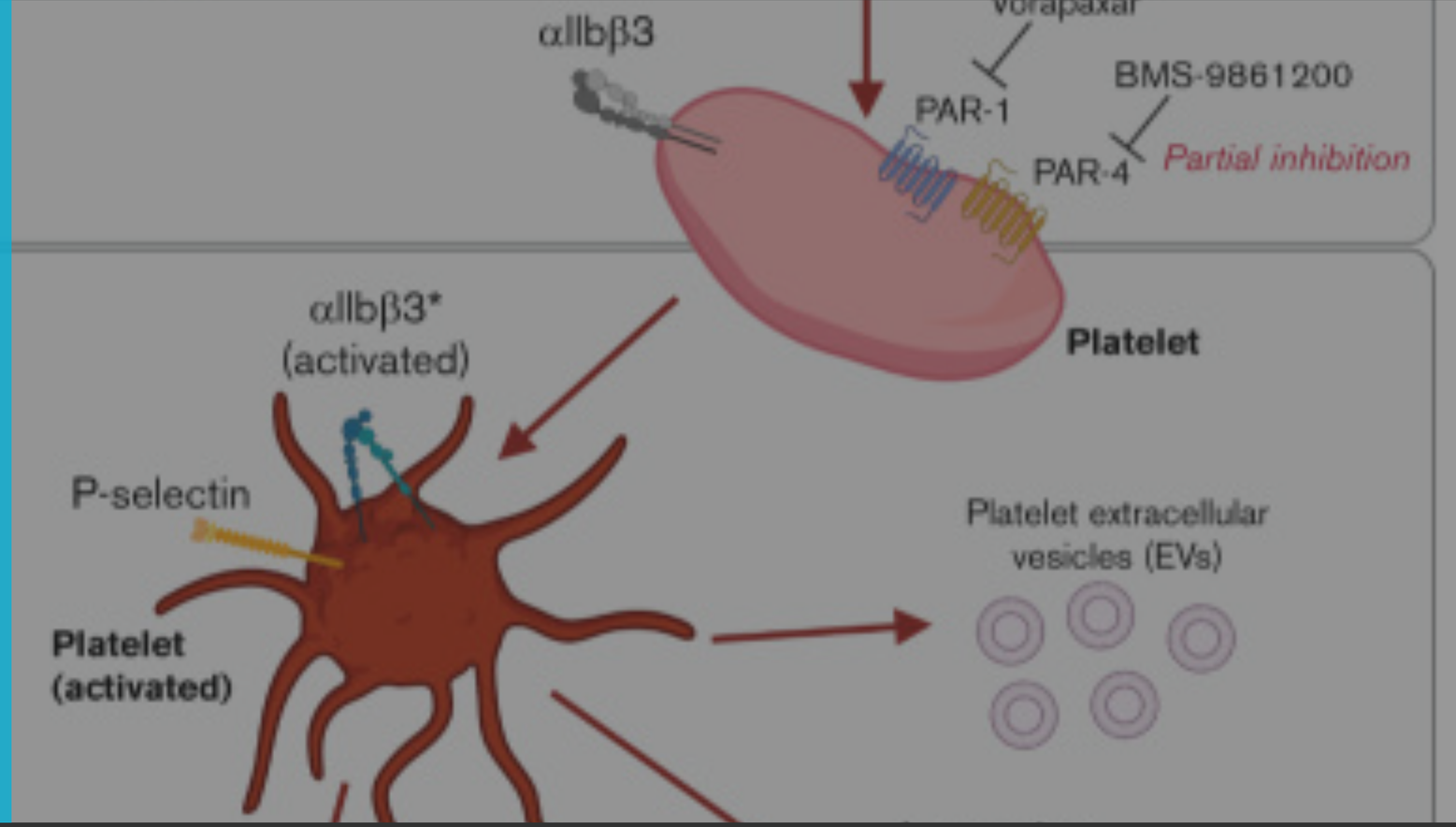
Nuclear factor-κB is a protein complex that serves as a key transcription factor in inflammation. It is found in all nucleated cells in the body and is one of the **primary, preserved** regulatory inflammatory signals within the body. Together with the SARS-CoV-2 virus, NF-κB signaling, **increases systemic inflammation, cytokine storm, adverse events,** and **mortality risk.**



link between NF-κB transcription and cancer is associated with an **increase** in **cancer development, progression, and metastasis**. Specifically, NF-κB plays a role in: 1) **carcinogenesis,** 2) **malignant transformation,** 3) **oncogenic metabolism,** 4) **alteration of the Tumor Microenvironment (TME),** 5) **inhibition of apoptosis (programmed cell death),** 6) **promotion of angiogenesis,** 7) **proliferation,** 8) **invasion,** 9) **immune evasion and escape,** 10) **Epithelial to Mesenchymal Transition (EMT),** 11) **metastasis,** 12) **chemoresistance,** 13) **radiation resistance and** 14) **cancer cell stemness**. It is the upregulation of NF-κB transcription that is responsible for upregulation of many cytokines, including interleukin (IL)-6, IL-1β, tumor necrosis factor α (TNF-α), and interferons—called **cytokine storm**. More, it is responsible for upregulation and cooption of JAK/STAT signaling; aberrant hyperactivation of the JAK/STAT pathway has been shown to result in chronic inflammatory signaling and/or various types of cancer. (from *Zong Z, Wei Y, Ren J, Zhang L, Zhou F. The intersection of COVID-19 and cancer: signaling pathways and treatment implications*.)

Platelets

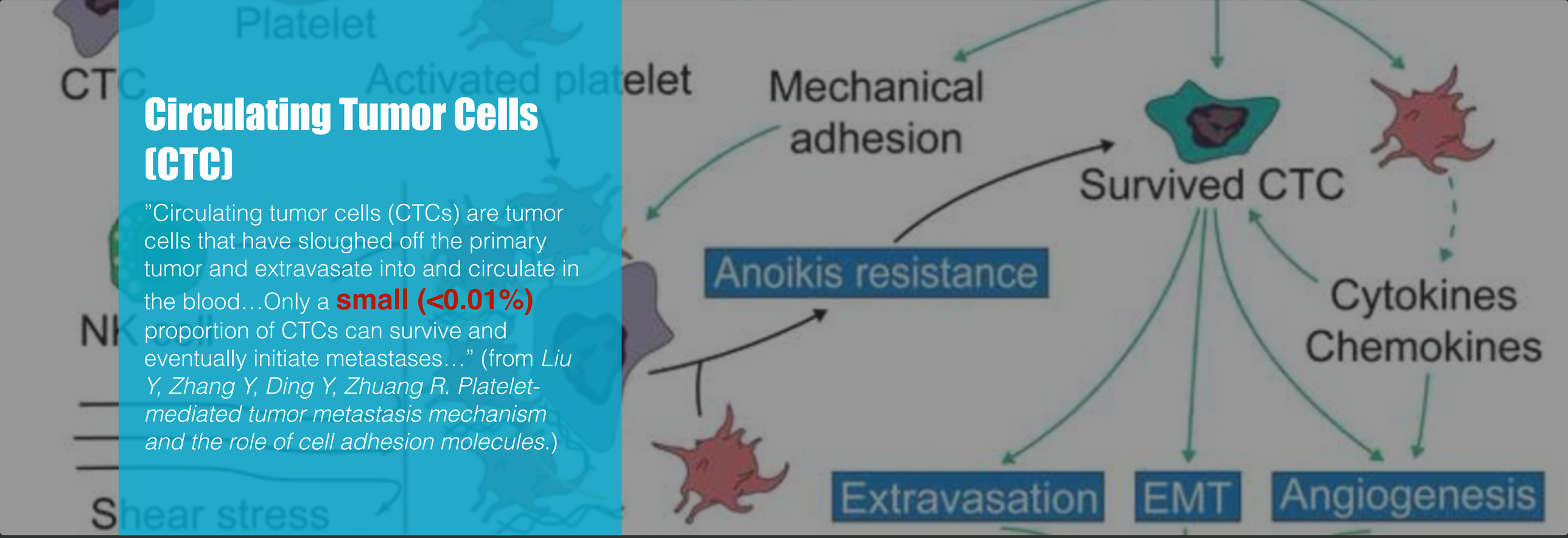
Platelets are critically involved in the process of **metastasis**. Platelets are generally known for their assistance in clotting. But, in cancer, platelets are **co-opted**, and their function is **adulterated** to help promote **carcinogenesis**, specifically **metastasis**.



"…observations that link **platelets**, COVID-19 and malignancy suggest the possibility that altered platelet physiology in SARS-CoV-2 infected cancer patients could **adversely exacerbate** the **progression** and **metastatic spread** of cancer and a potential therapeutic role for anti-platelet agents in altering the course of the disease." (from *Lichtenberger LM, Vijayan KV.. Is COVID-19-Induced Platelet Activation a Cause of Concern for Patients with Cancer?*) Platelets help to **export** the **tumor microenvironment (TME)** within the circulating **platelet—cancer cell aggregate** and represent a clear and present danger in cancer patients.

Circulating Tumor Cells (CTC)

”Circulating tumor cells (CTCs) are tumor cells that have sloughed off the primary tumor and extravasate into and circulate in the blood…Only a **small (<0.01%)** proportion of CTCs can survive and eventually initiate metastases…” (from *Liu Y, Zhang Y, Ding Y, Zhuang R. Platelet-mediated tumor metastasis mechanism and the role of cell adhesion molecules.*)

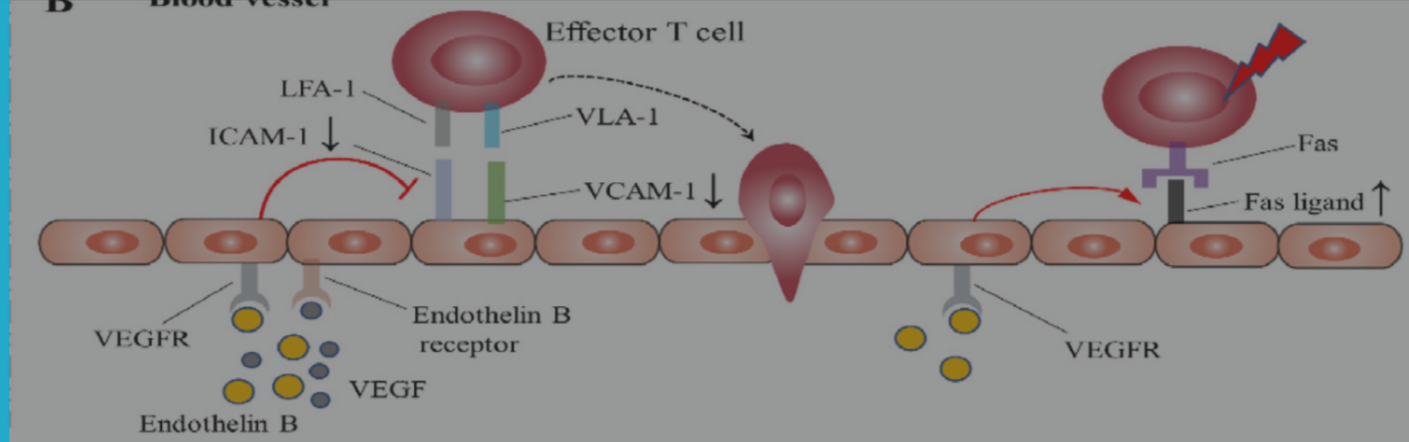


“Platelets have been shown to **promote survival** of circulating tumor cells (CTCs) in the bloodstream by conferring **resistance** to the 1) **shear stress** and 2) attack from **natural killer cells**. Recently, platelets were found to **promote and/or maintain** the state of epithelial to mesenchymal transition on CTCs through platelet secretion of transforming growth factor β in response to CTC activation. At a later stage in the metastatic process, **platelets promote extravasation, intravasation, and establishment of metastatic cells in distant organs** as observed in bone.” (from *Liu Y, Zhang Y, Ding Y, Zhuang R. Platelet-mediated tumor metastasis mechanism and the role of cell adhesion molecules.*)

Immune Escape

Immune escape is one of the **key critical gateways** forward in **carcinogenesis, cancer progression, and metastasis.**

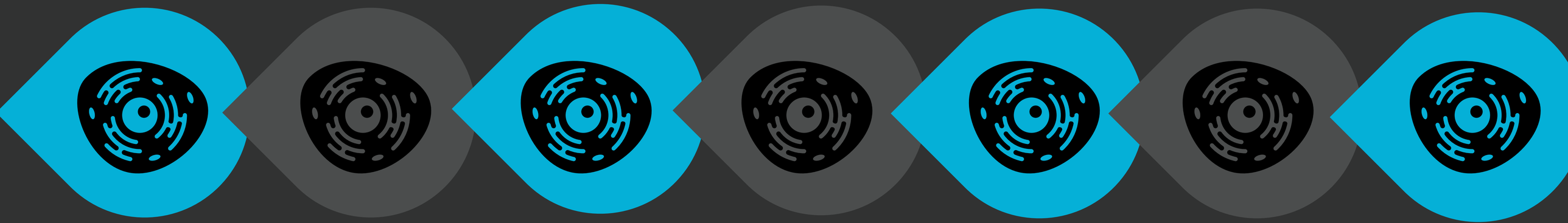
"Immune escape is the terminal stage of immunoediting, a process that coevolves with oncogenesis." Immune system abnormalities, i.e., dendritic cells, T cells and tumor cells, prevent the immune system recognition and destruction of cancer cells; ultimately resulting in an immunosuppressive microenvironment, via Tregs, TAMs and MDSCs, CTLA4, and PD-1.



LPS induced metabolic endotoxemia beget **comorbidity, comorbidity** begets risk from **SARS-CoV-2 virus.** But, the two together, **LPS and SARS-CoV-2 spike protein,** increase the **NF-κB** inflammation signaling by **50%** compared to each individually. It is the same NF-κB inflammatory signaling, in cancer cells and in the tumor microenvironment that enhances cancer cell growth, survival, genetic and epigenetic alterations, oncogenic metabolic transformation, acquisition of cancer stem cell properties, epithelial-to-mesenchymal transition, invasion, angiogenesis, **immune escape**, metastasis, treatment resistance, and suppression of anti-tumour immunity. Whatever the source of the SARS-CoV-2 spike protein (infection or injection), coupled with the background of LPS mediated metabolic endotoxemia that research has established pre-exists, the stage is set for a logical expectation of increased carcinogenesis, rapid growth, metastasis, treatment resistance, and recurrence now and in the future—**Cancer is the coming next Pandemic.** (from *Tang S, Ning Q, Yang L et al. Mechanisms of immune escape in the cancer immune cycle.*)

Immunomodulation

Selective use of substances, often called biological response modifiers, to intentionally stimulate or suppress immune system activity; often used in the treatment of cancer, infections, and autoimmune disease.



Hyperinflammation

Cytokine storm

NETosis

Elevated
Neutrophil
Lymphocyte

Elevated
Platelet
Lymphocyte

mRNA Trigger
of TLR4

Autoimmunity

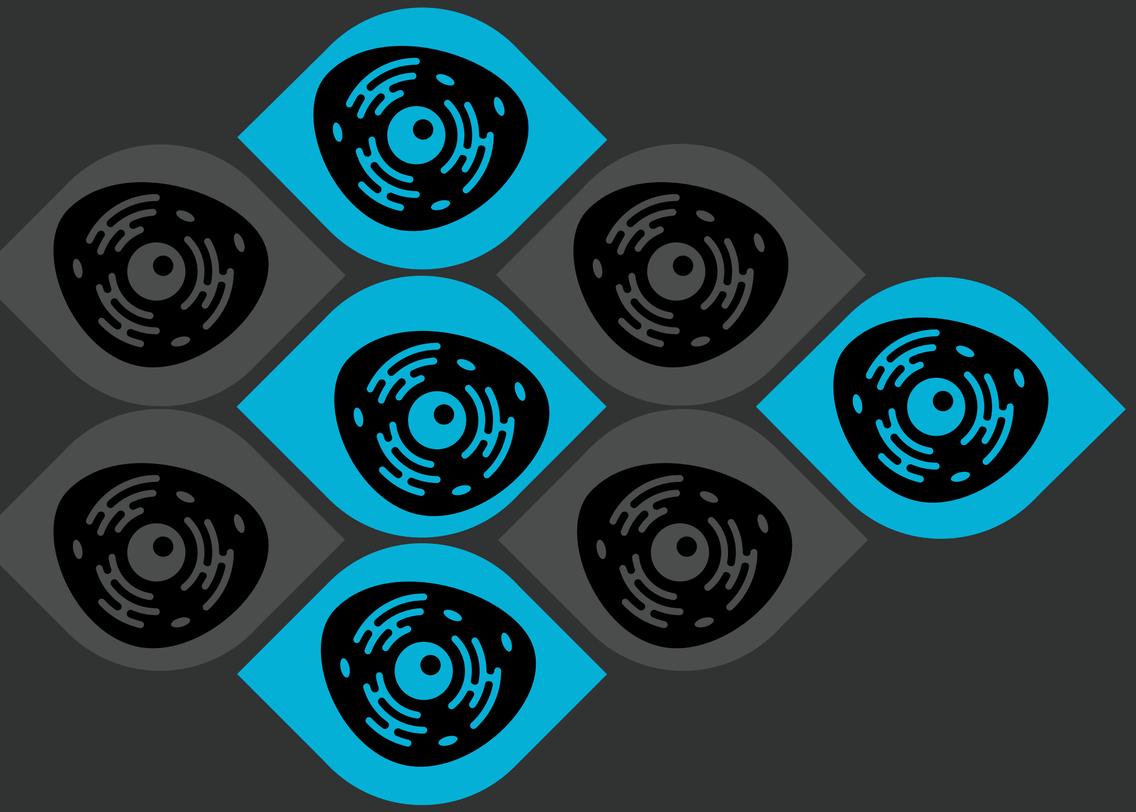
Tumor suppression

Tumor Immunoediting

Tumor promotion

Immunomodulation

Selective use of substances, often called biological response modifiers, to intentionally stimulate or suppress immune system activity; often used in the treatment of cancer, infections, and autoimmune disease.



Hyperinflammation

A form of very severe inflammation accompanied with cytokine storm

Cytokine Storm

Results from an out of control, hyper activated immune system response resulting from infectious and non-infectious sources.

NETosis

Neutrophils generate extracellular fibers, or neu- trophil extracellular traps (NETs), which are struc- tures composed of granule and nuclear constitu- ents that disarm and kill bacteria extracellularly

NLR

Peripheral biomarker of systemic inflammation to predict and direct treatment response as well as long-term outcomes.

PLR

Peripheral biomarker of systemic immune response adequacy and potential to predict and direct treatment response as well as long-term outcomes.

TLR4

Spike glycoprotein binds and activates the transmembrane protein, TLR4, a transmembrane protein, increasing downstream hyperinflammatory cytokine signaling.

Autoimmune

Cancer, in many ways, is an autoimmune disease process whereby the immune system turns its attack on the very defense of the immune system.

Hyperinflammation Defined and Referenced

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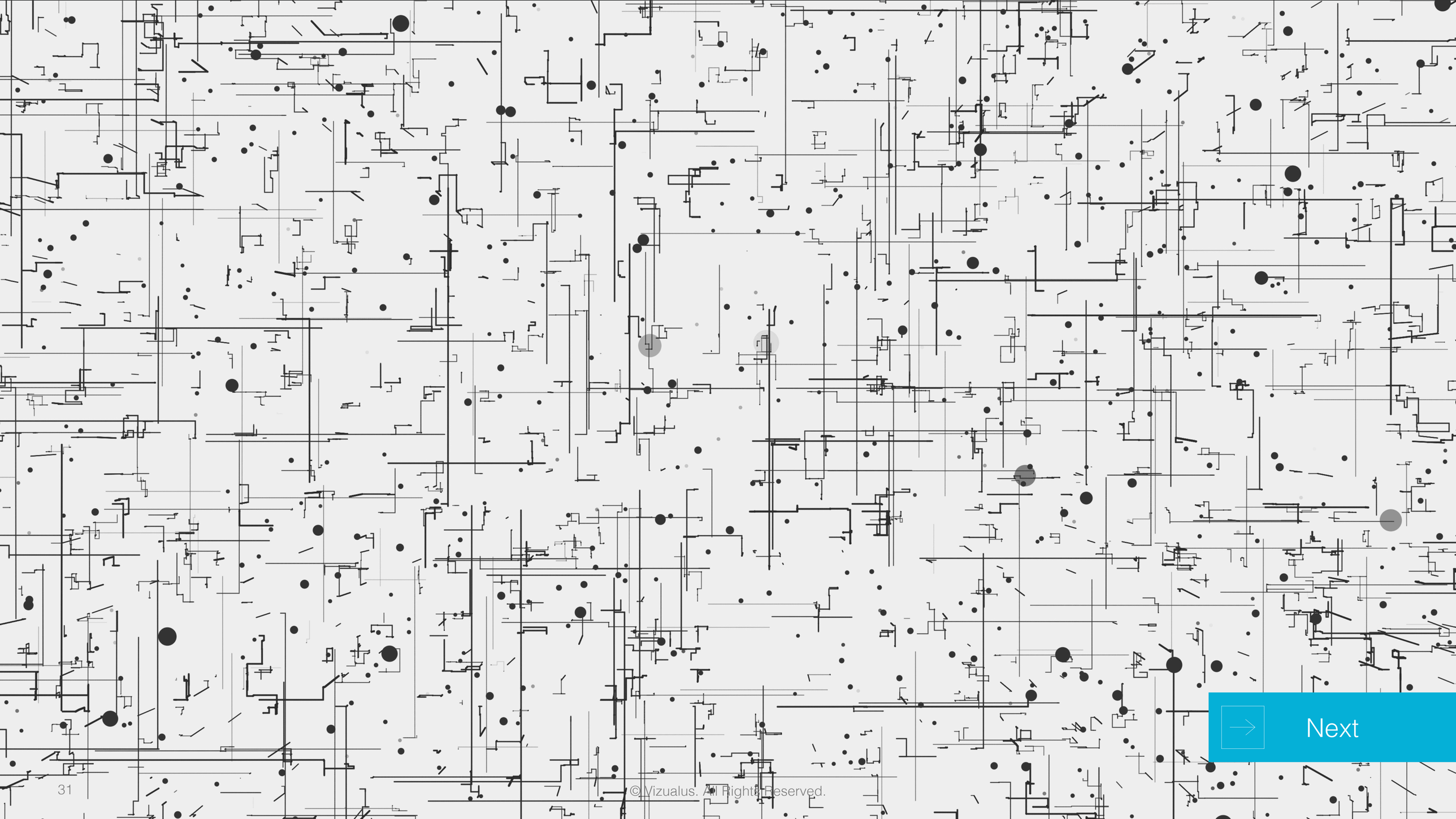

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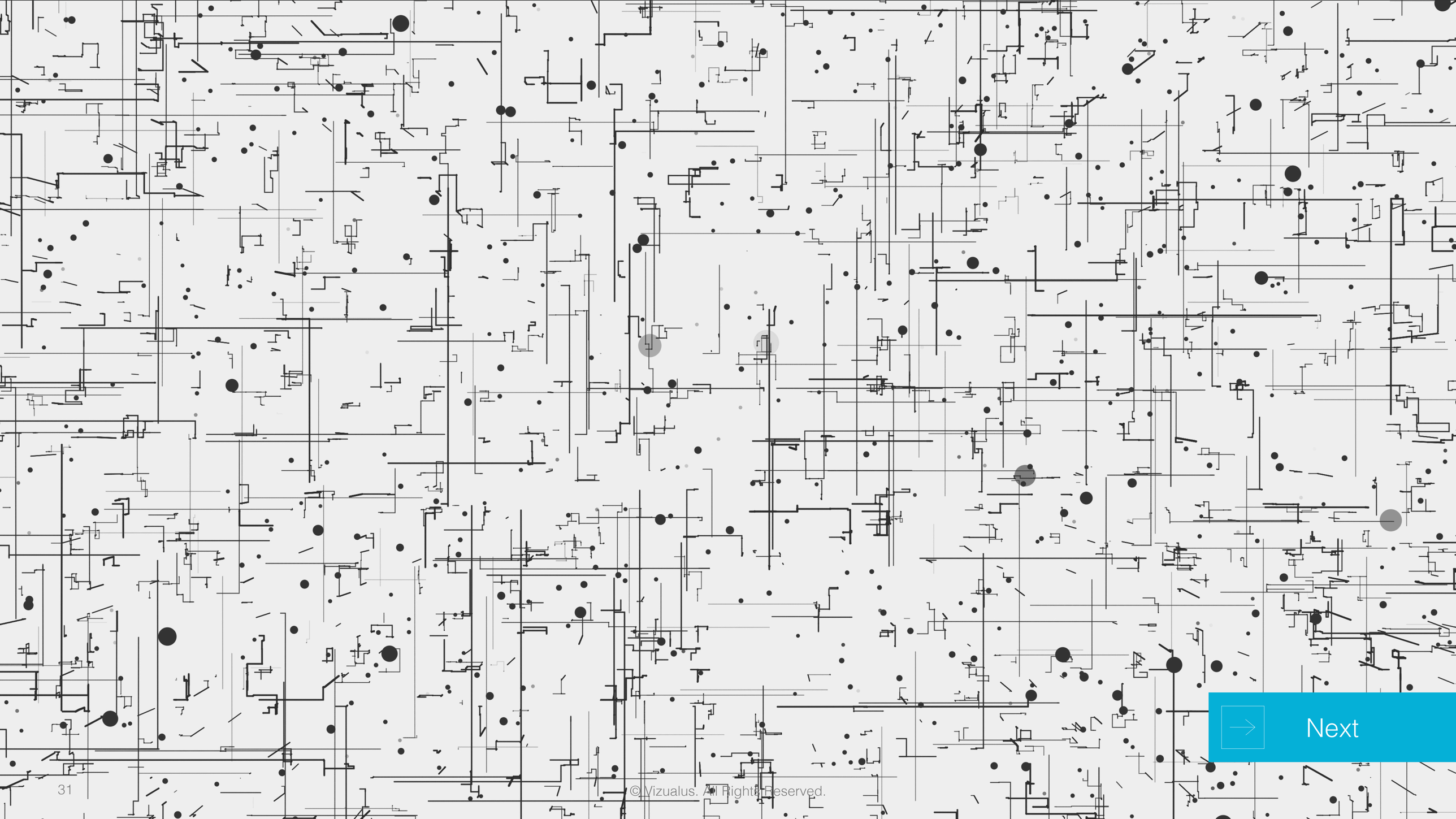

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SARS-CoV-2

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SARS-CoV-2 · Inflammation ·

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SARS-CoV-2 · Inflammation · Cancer

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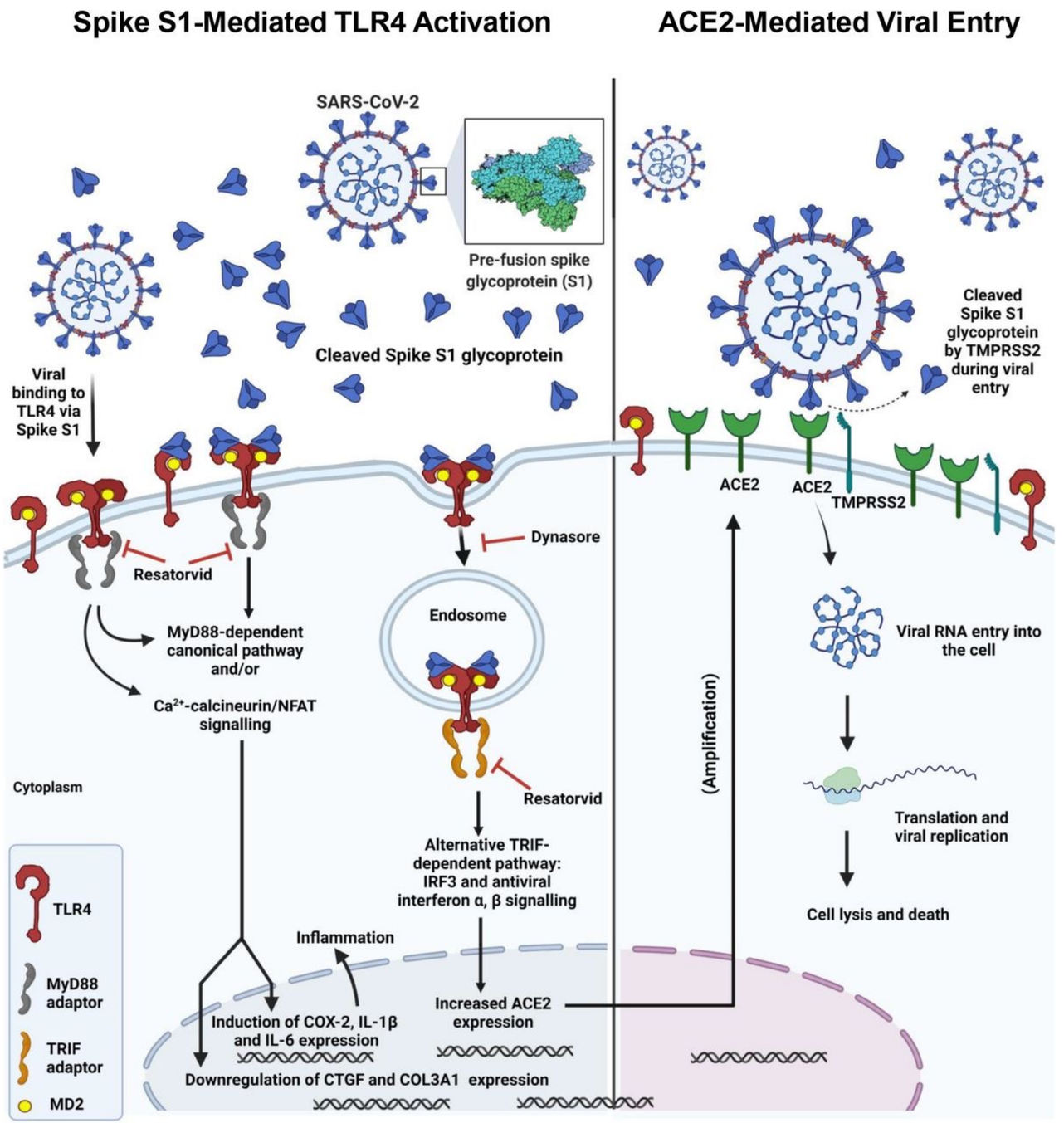

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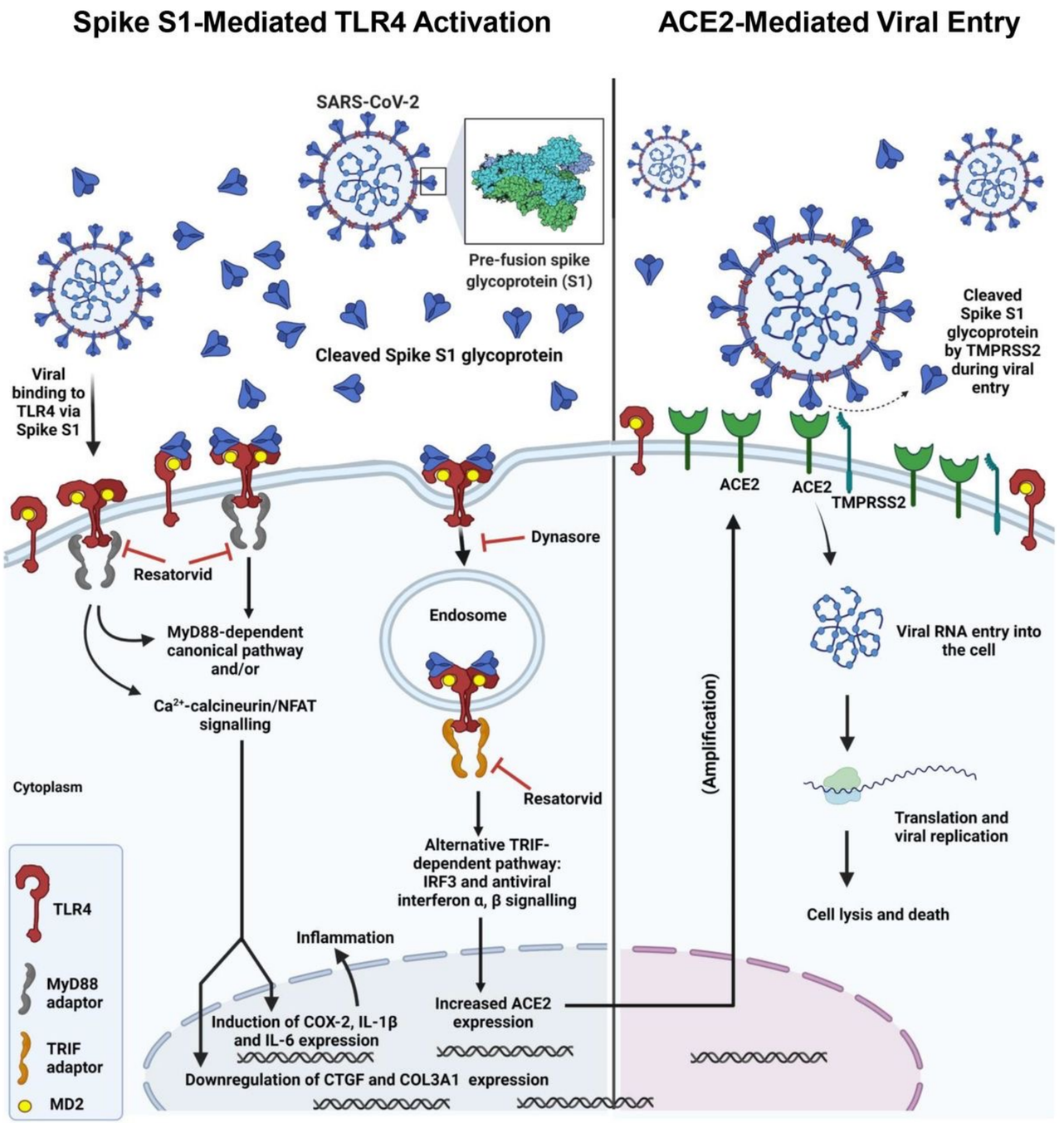

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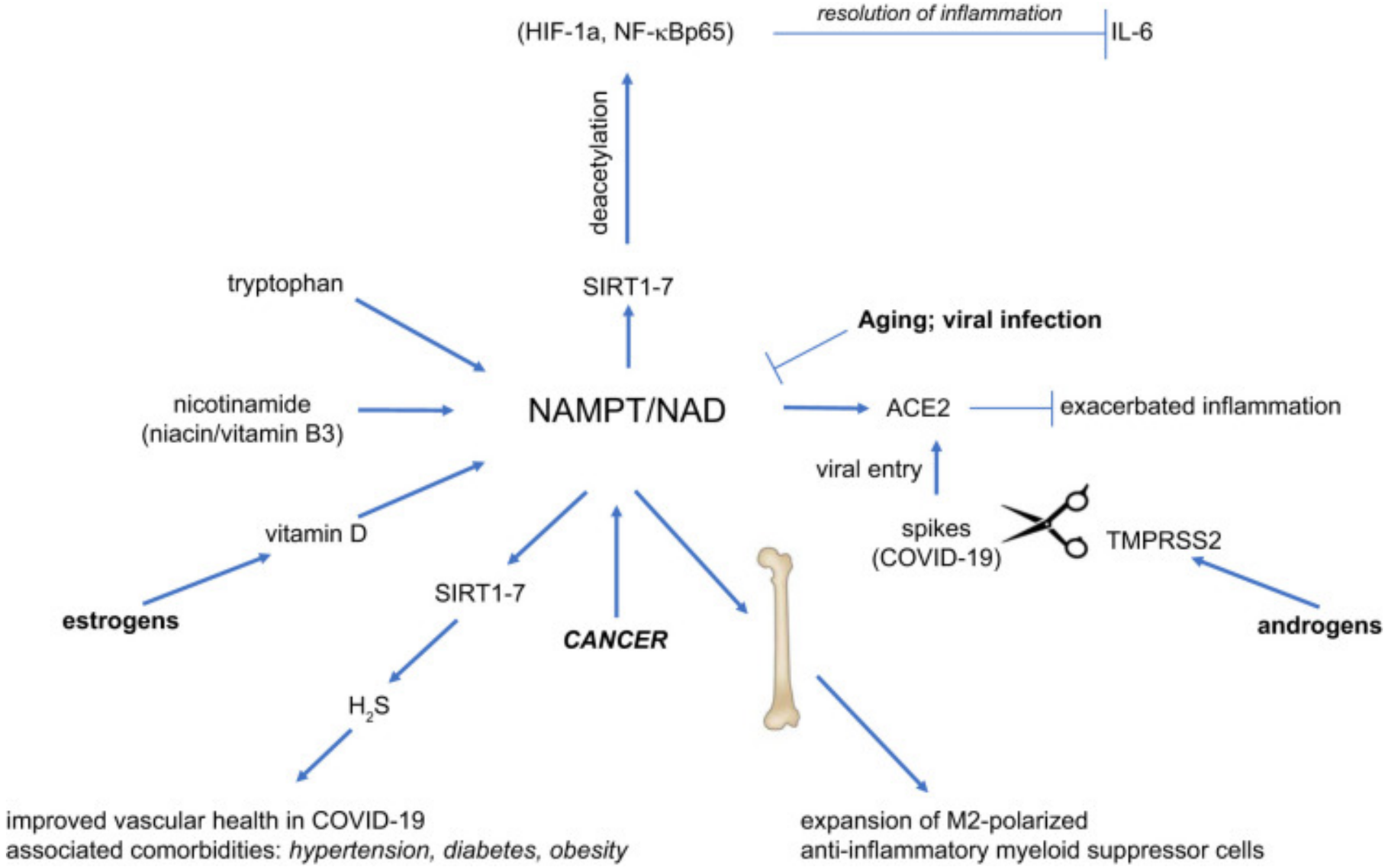

Sica A, Colombo MP, Trama A et al. Immunometabolic Status of COVID-19 Cancer Patients

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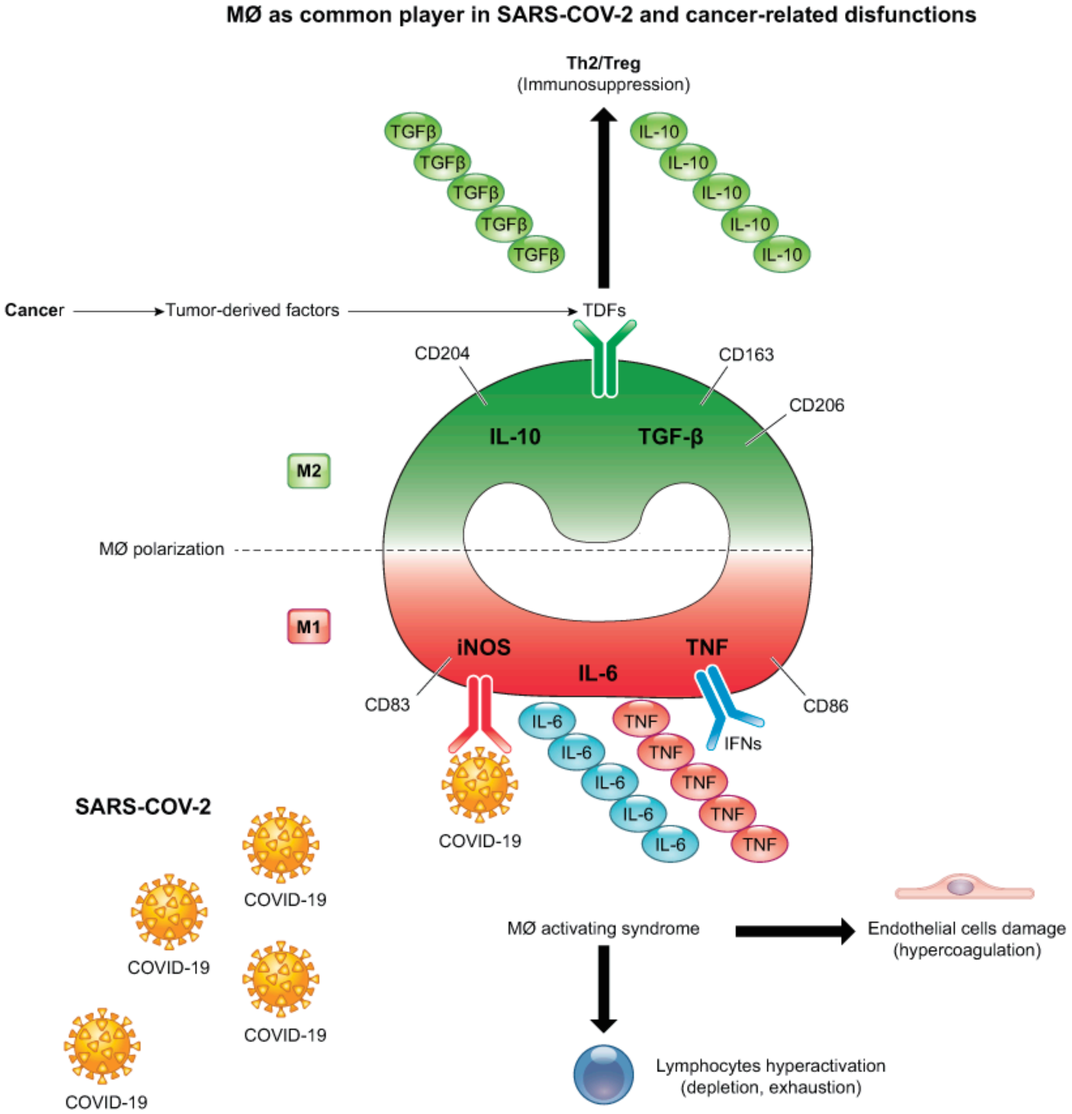
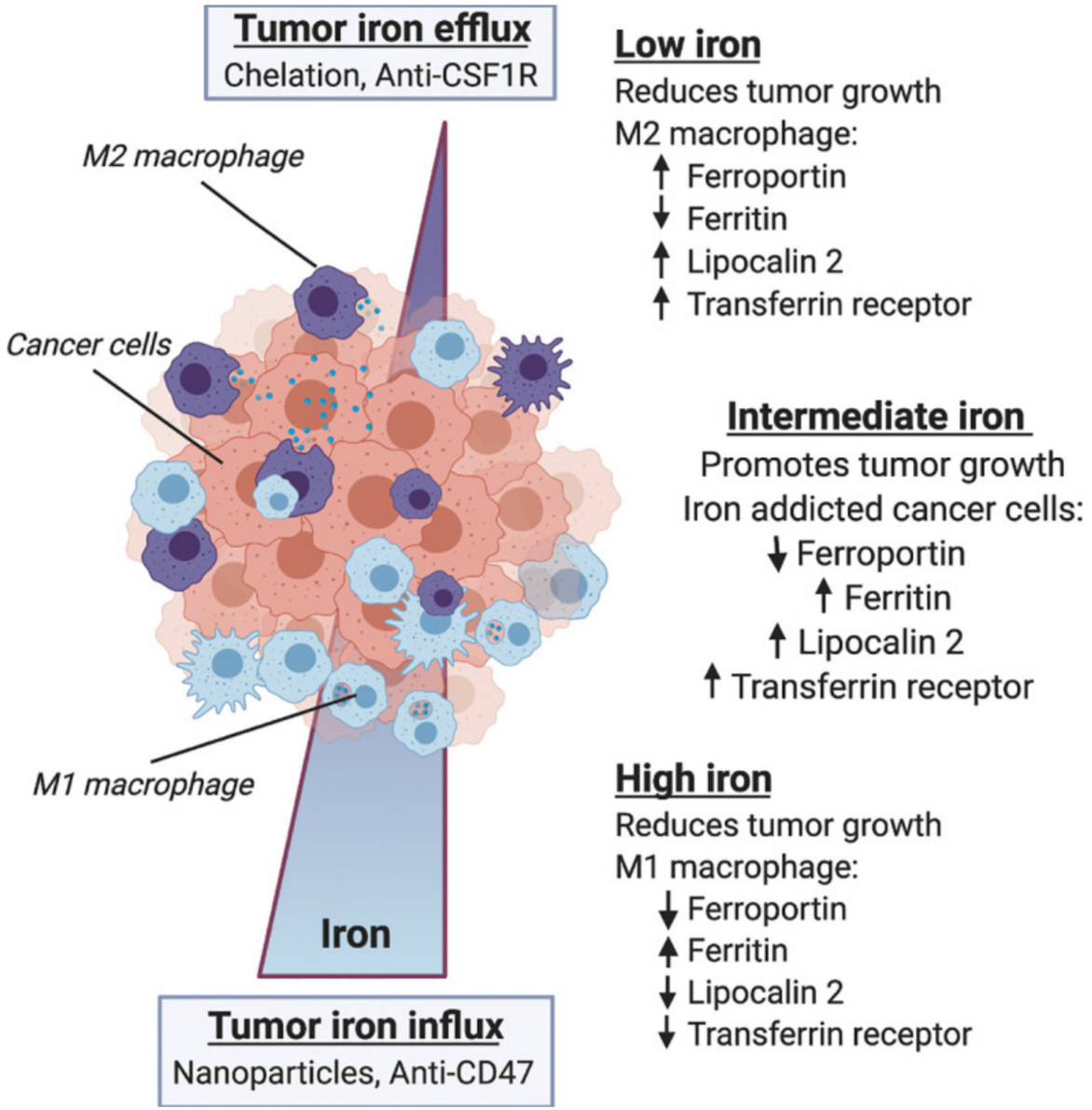


Immunometabolic Status of COVID-19 Cancer Patients

Tumor Microenvironment Gradient

Normoxia	Hypoxia
M1	M2
Fe storage	Fe Release

Angiogenesis, invasion, metastasis, Poor survival



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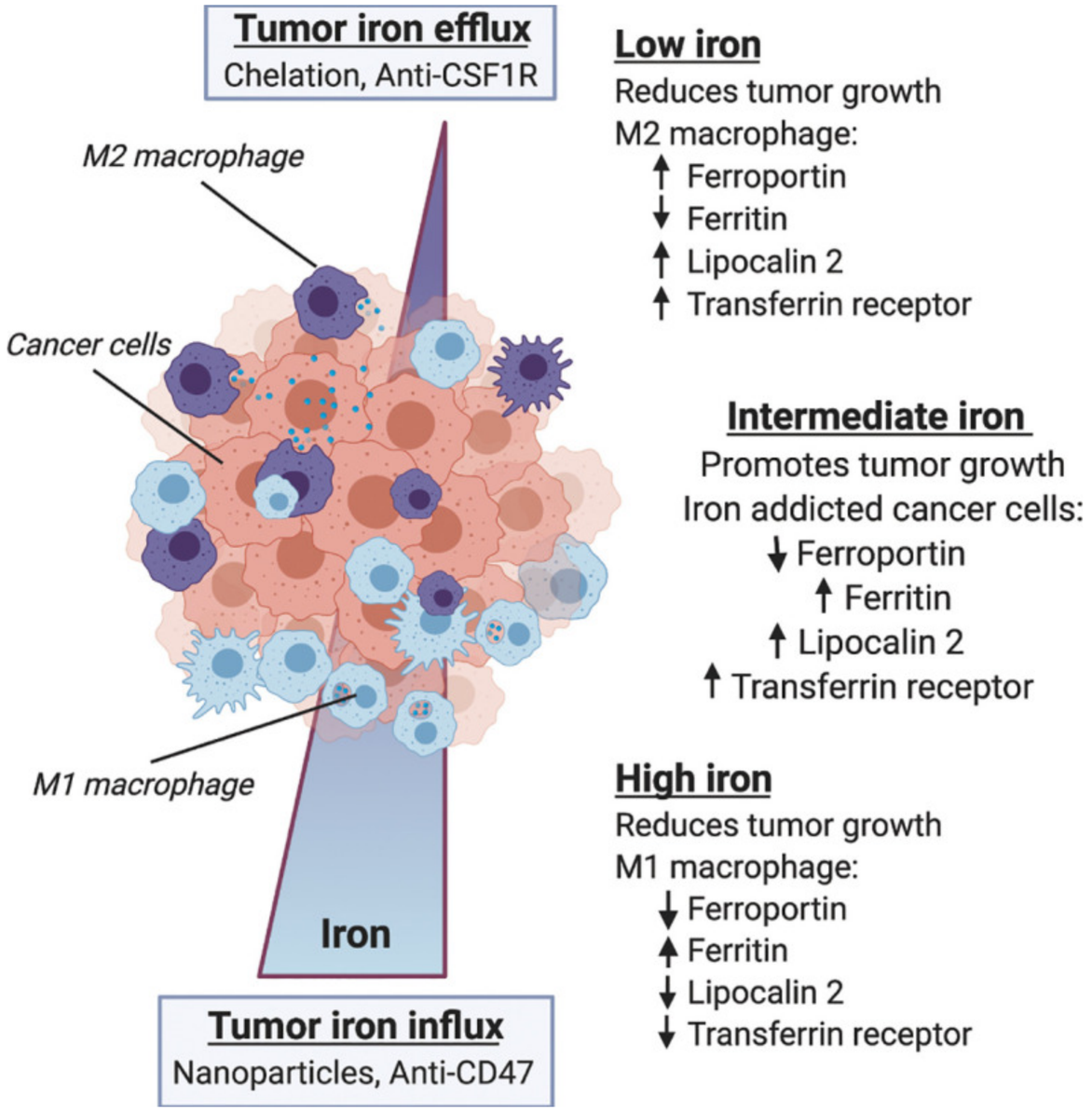

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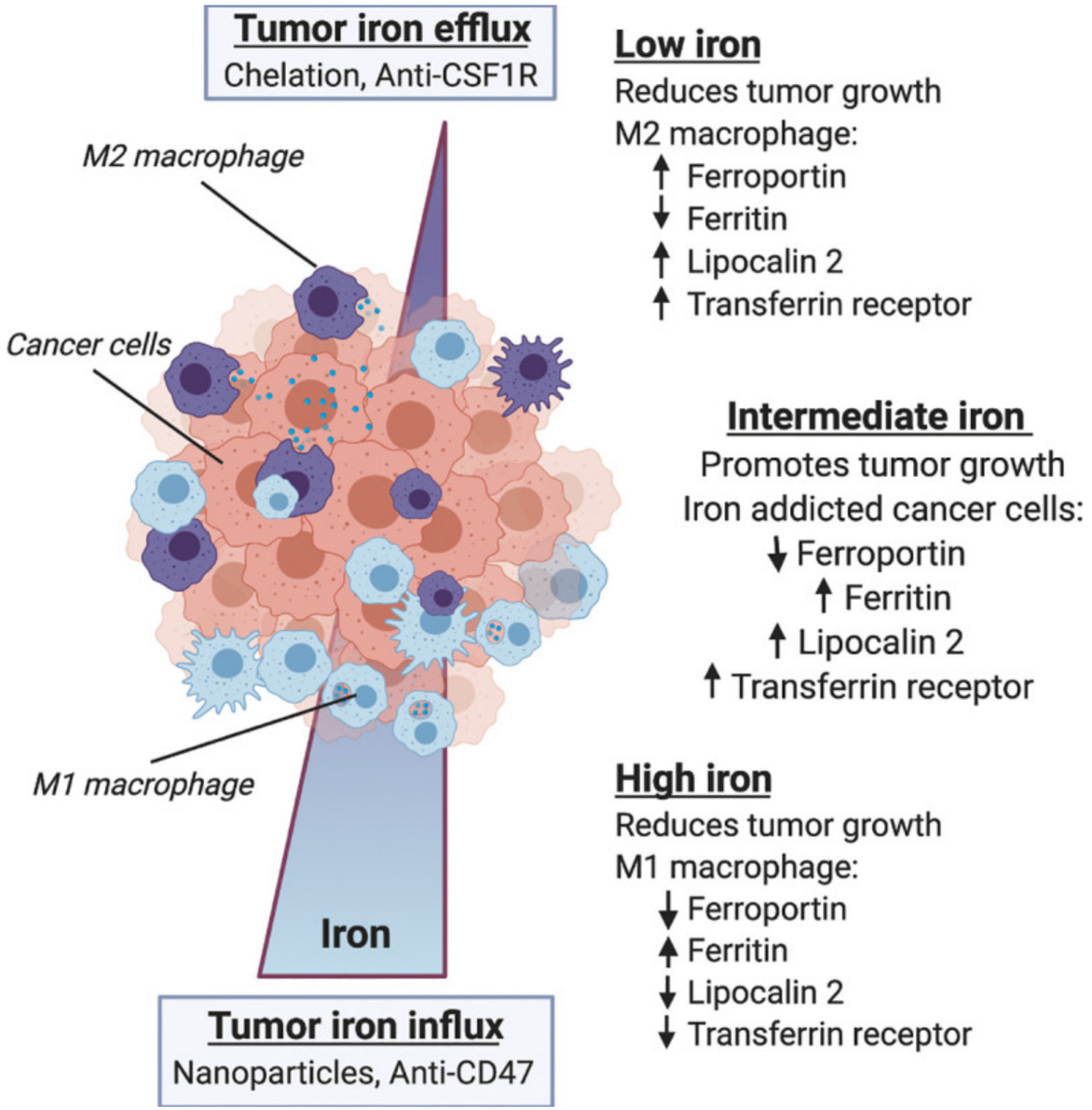

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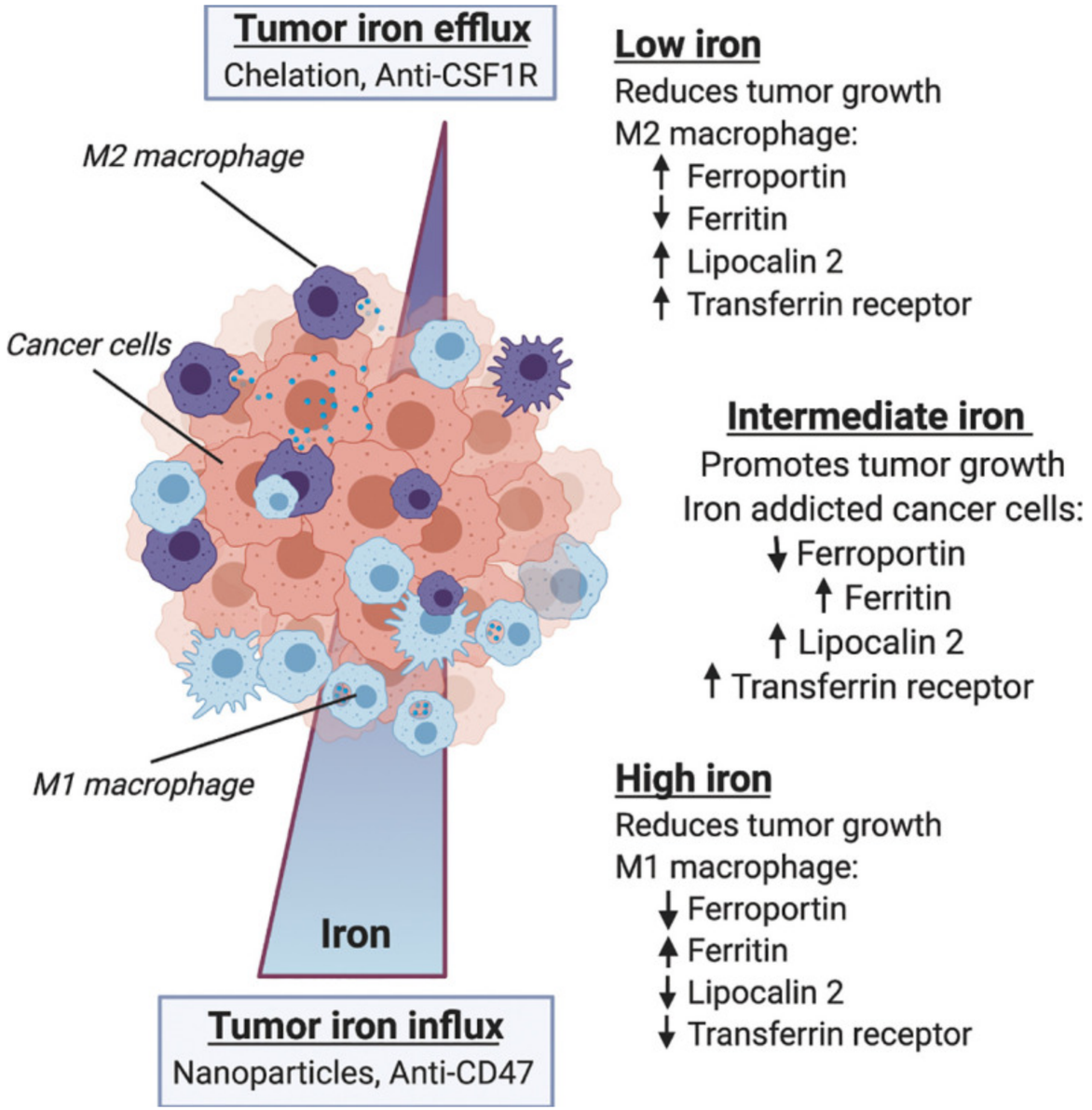

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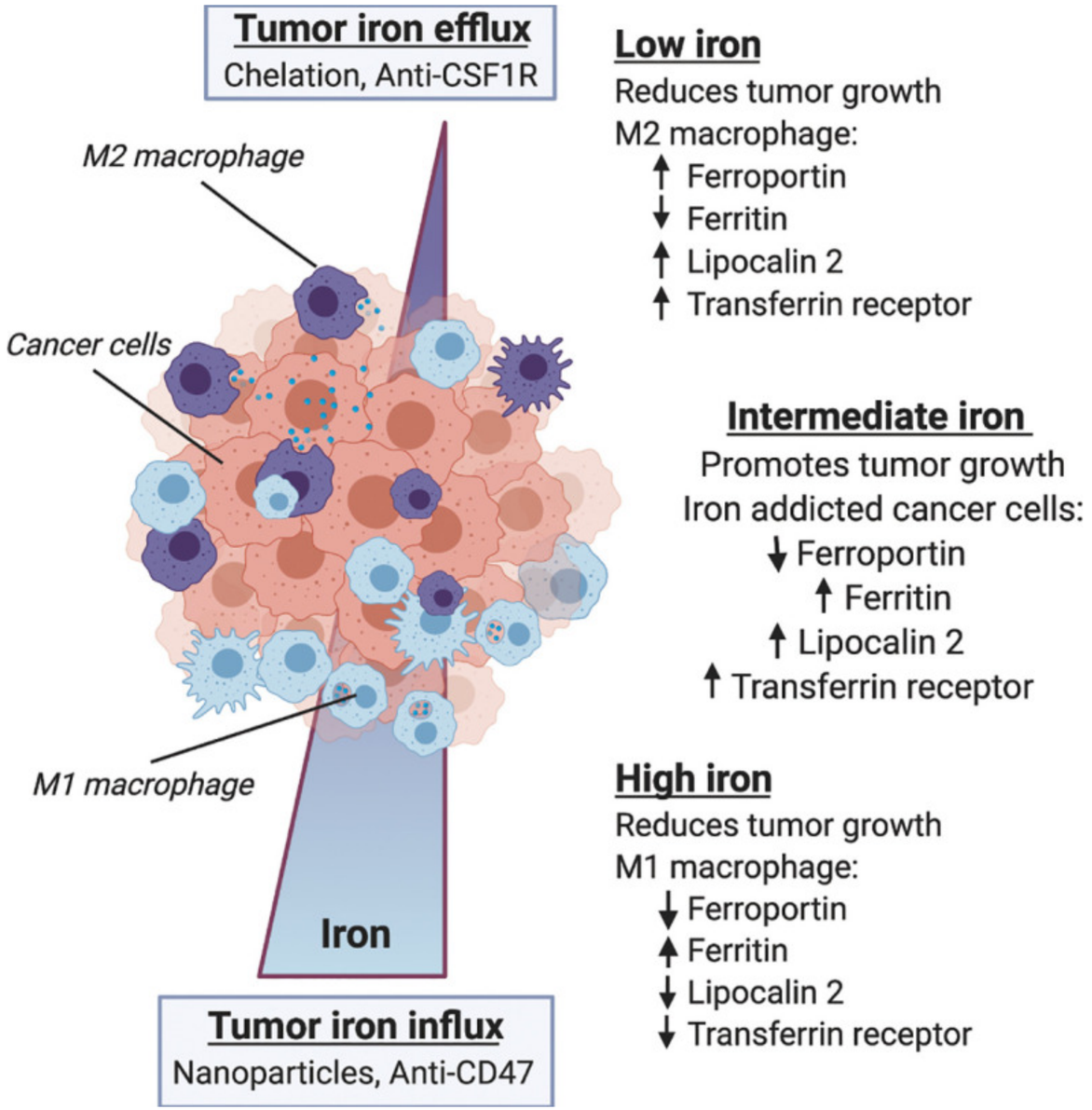

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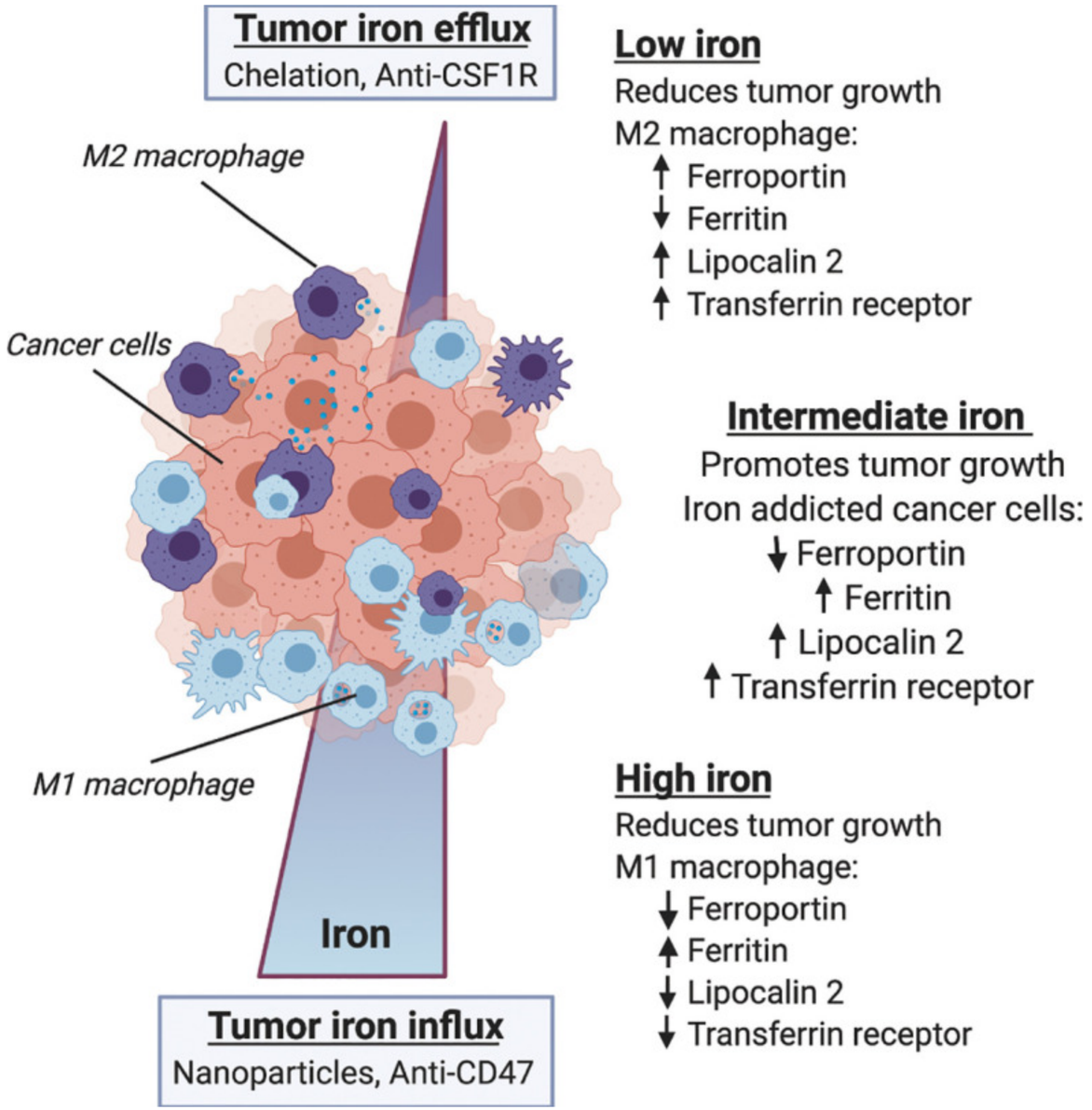
Cancer Progression

Late

Early



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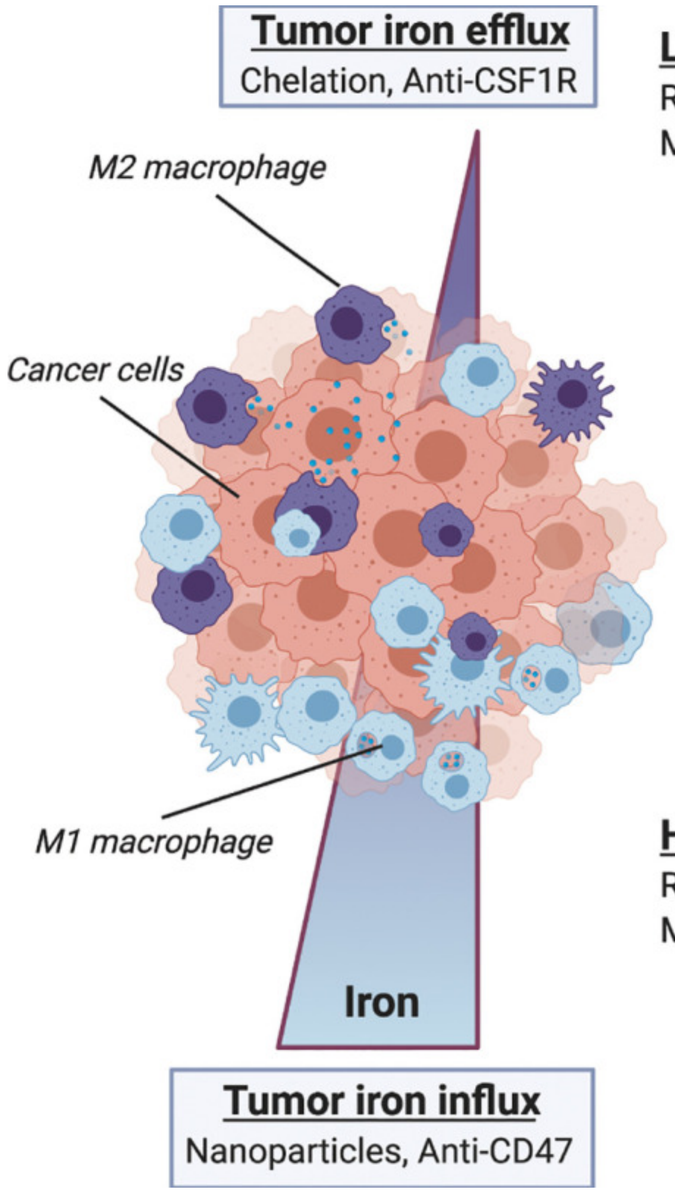

Low iron
Reduces tumor growth
M2 macrophage:
- ↑ Ferroportin
- ↓ Ferritin
- ↑ Lipocalin 2
- ↑ Transferrin receptor

Intermediate iron
Promotes tumor growth
Iron addicted cancer cells:
- ↓ Ferroportin
- ↑ Ferritin
- ↑ Lipocalin 2
- ↑ Transferrin receptor

High iron
Reduces tumor growth
M1 macrophage:
- ↓ Ferroportin
- ↑ Ferritin
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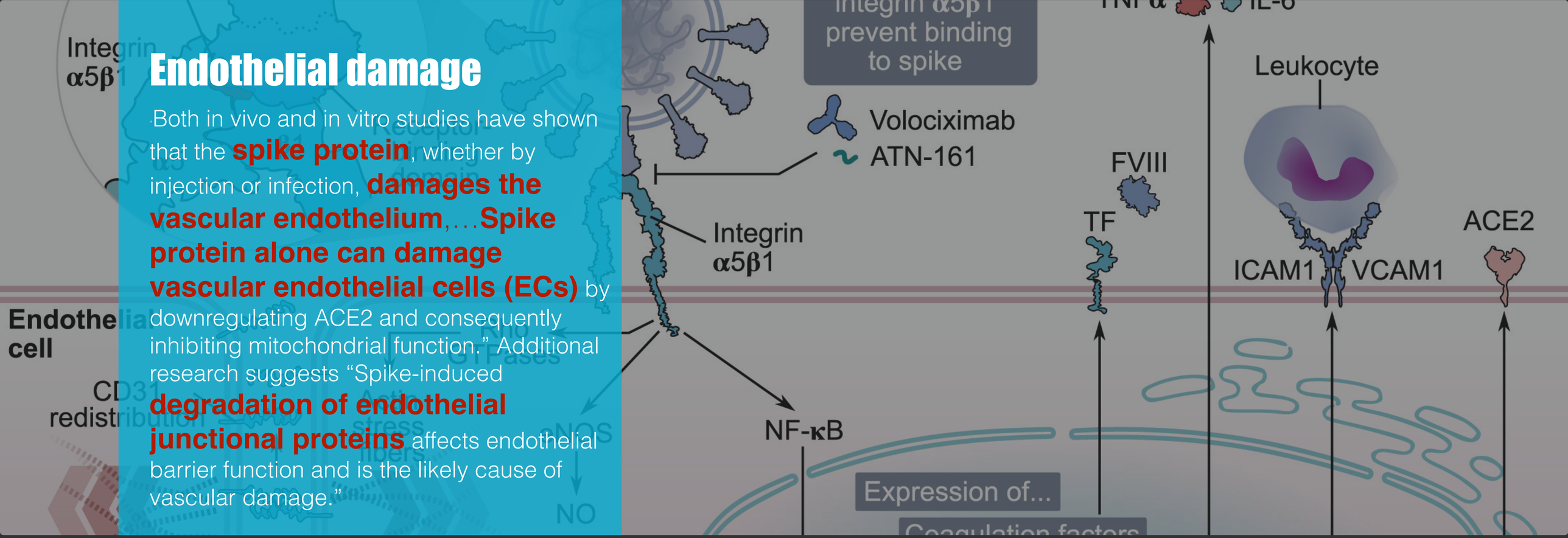
Endothelial damage

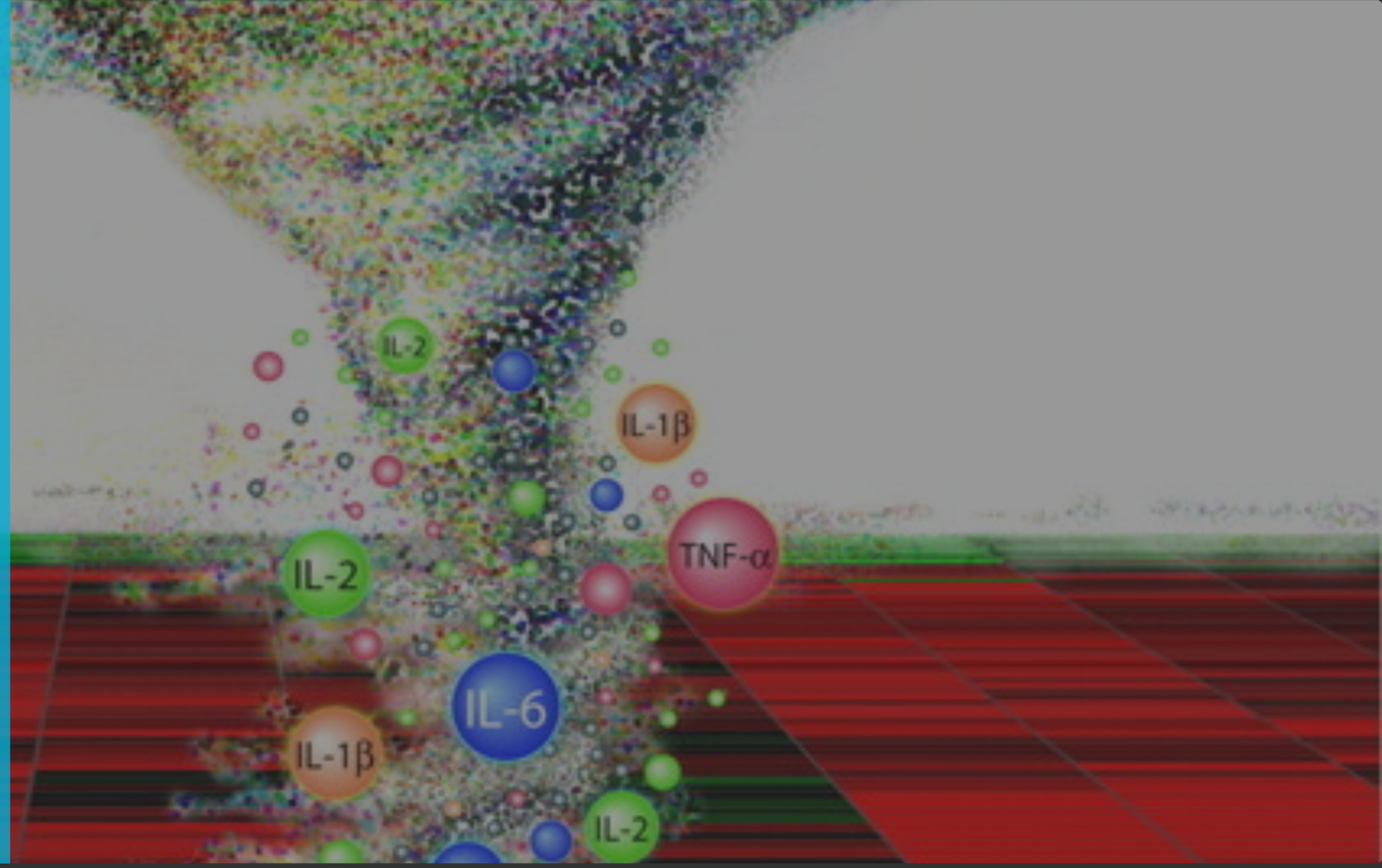
Both in vivo and in vitro studies have shown that the **spike protein**, whether by injection or infection, **damages the vascular endothelium**,…**Spike protein alone can damage vascular endothelial cells (ECs)** by downregulating ACE2 and consequently inhibiting mitochondrial function." Additional research suggests "Spike-induced **degradation of endothelial junctional proteins** affects endothelial barrier function and is the likely cause of vascular damage."



"Once inside the host cells, SARS-CoV-2 induces acute respiratory distress syndrome (ARDS), stimulates immune response (i.e., cytokine storm) and **vascular damage**. **SARS-CoV-2 induced endothelial cell injury** could **exacerbate endothelial dysfunction**, which is a hallmark of aging, hypertension, and obesity, leading to further complications". **Cancer** and thromboembolism would fall into the "further complications". (from *Lei Y, Zhang J, Schiavon CR et al. SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2.*)

Metastasis

Connecting the dots:

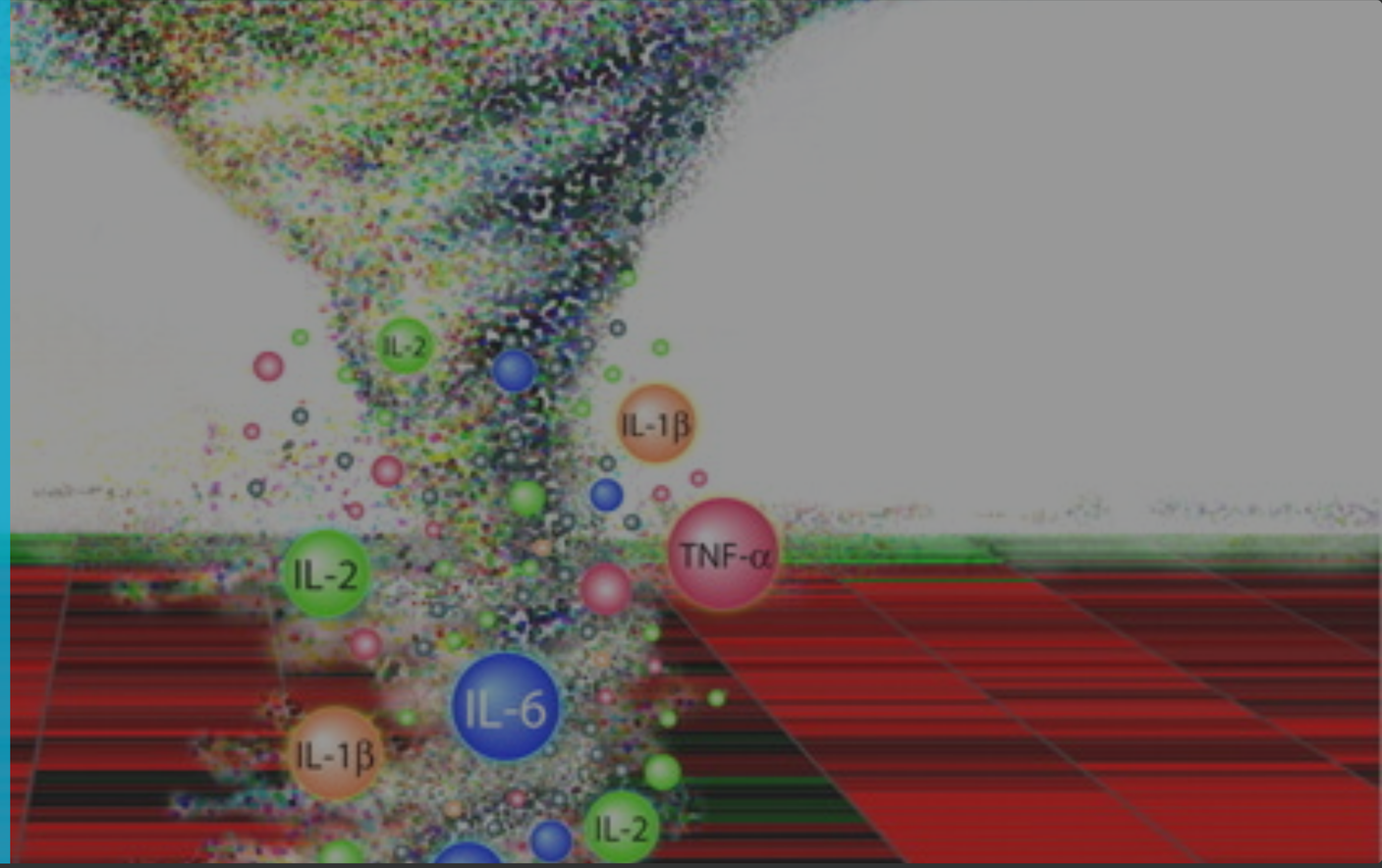


It is essential to understand that the endothelium is at the center of this wheel of the dysfunction cascade that leads to metastasis. Whatever the source of the spike protein, (infection, injection, or repeated injection) research points to an 1) increase in endothelium **damage and dysfunction**, 2) platelet **hyperactivity**, 3) **angiogenic** potential, 4) cancer cell **extravasation**, 5) **increased platelet—cancer cell aggregation**, 6) immune **evasion**, 7) circulating tumor cell **survival**, 8) natural killer cell **suppression**, 9) cancer cell **intravasation** and 10) **micrometastasis**, which all point to an increase in 11) **macrometastasis**. The result will be an increase in cancer incidence, recurrence, metastasis, morbidity, and mortality. (Image from *Tisoncik JR, Korth MJ, Simmons CP et al. Into the eye of the cytokine storm.*)

Metastasis

Connecting the dots:

- Altered cellular metabolism
- Mitochondrial damage
- Altered genetic expression
- Disrupted cellular signaling
- Proliferation
- Hypoxia
- Angiogenesis
- Lymphagenesis
- Acidic TME
- TME immune recruitment



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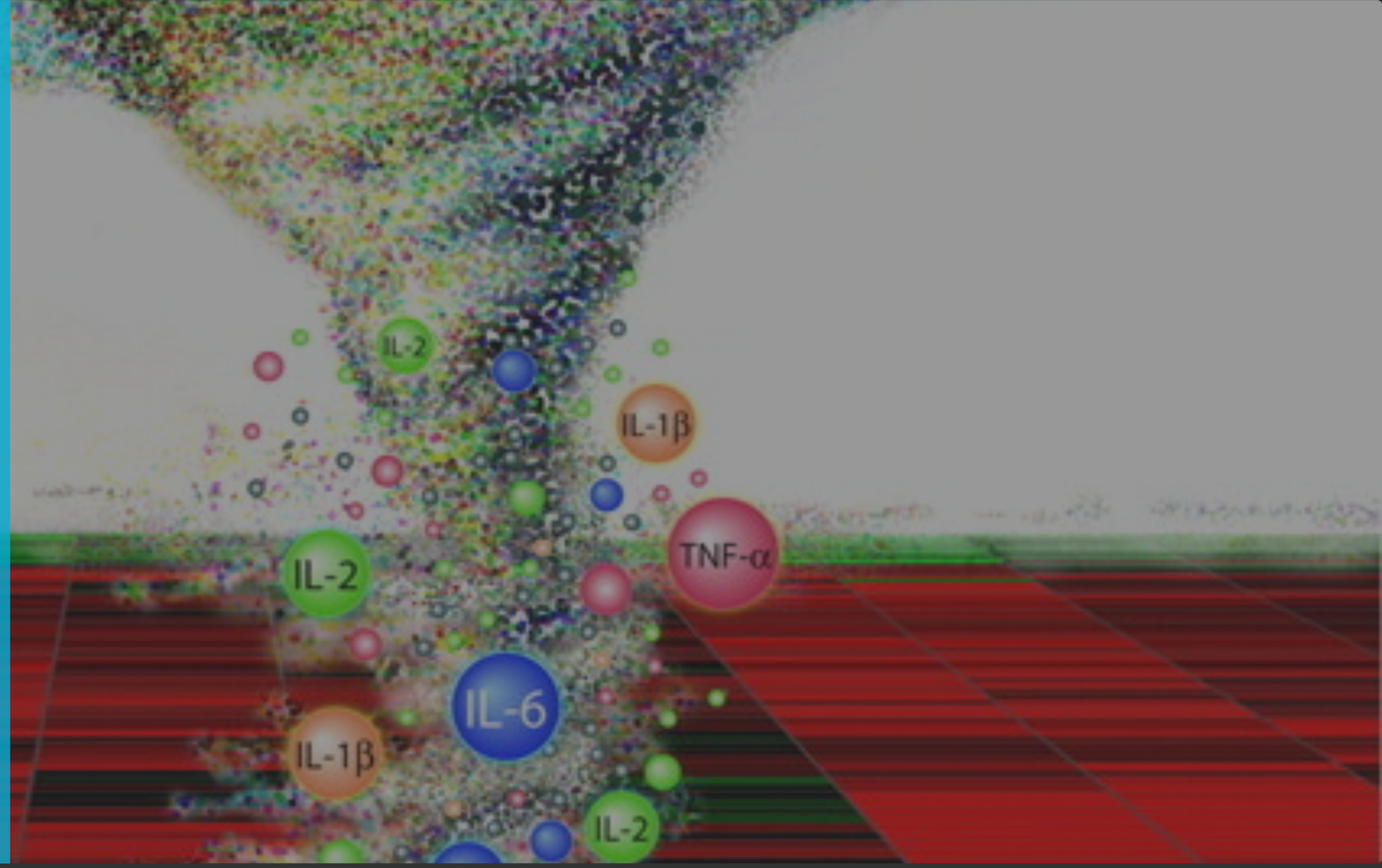
- Tumor escape
- Intravasation
- Dissemination
- Hypoxic memory
- Platelet cancer cell aggregate
- TME export
- Extravasation
- Metastasis



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Toxins
Spike proteins is, in fact, a toxin, or a toxicant depending on the source of origin.

2

TLR4
Receptors upregulated and activated in tumor microenvironment and cancer cells

1

3

Comorbidities
Visible evidence of chronic inflammation and disrupted immune function.

4

LPS
SARS-CoV-2 S protein binds to LPS boosting inflammatory response.

5

Receptors
ACE2 and integrin αvβ3 receptors serve as the gateway to the cell's internal machinery via the spike protein.

Platelets
Spike proteins hyperactivate platelets.

7

Circulating Tumor Cells (CTC)
Increased inflammatory signaling and immune escape increase CTC release and survival.

8

Immune Escape
Platelet-Cancer cell aggregates evade circulating immune surveillance.

9

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NF-κB signaling
SARS-CoV-2 viral Spike protein stimulate the same LPS mediated TLR Receptor to increase inflammatory signaling 50% above each individually

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Endothelium damage
Spike proteins directly cause endothelial damage.

Micrometastasis

Metastatic Map

90% of morbidity and mortality associated with cancer is when cancer spreads to distant organ sites—metastasis.

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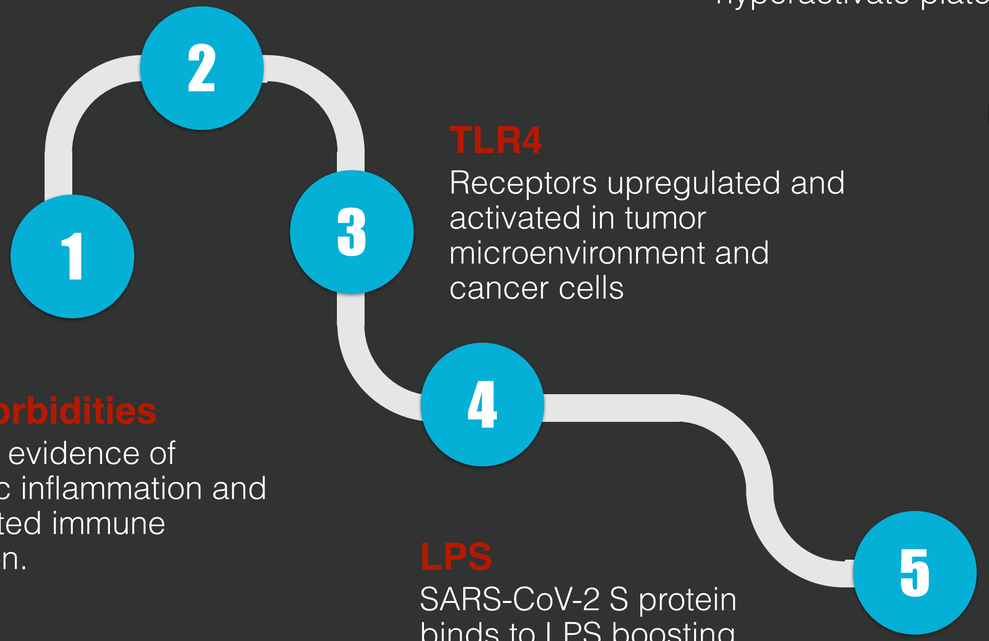

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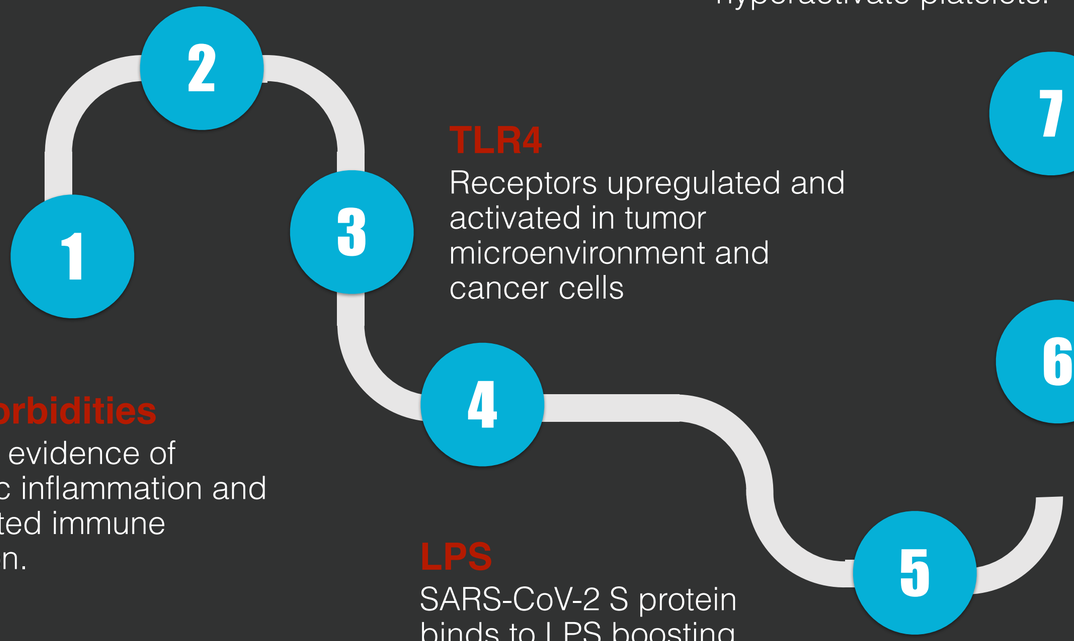

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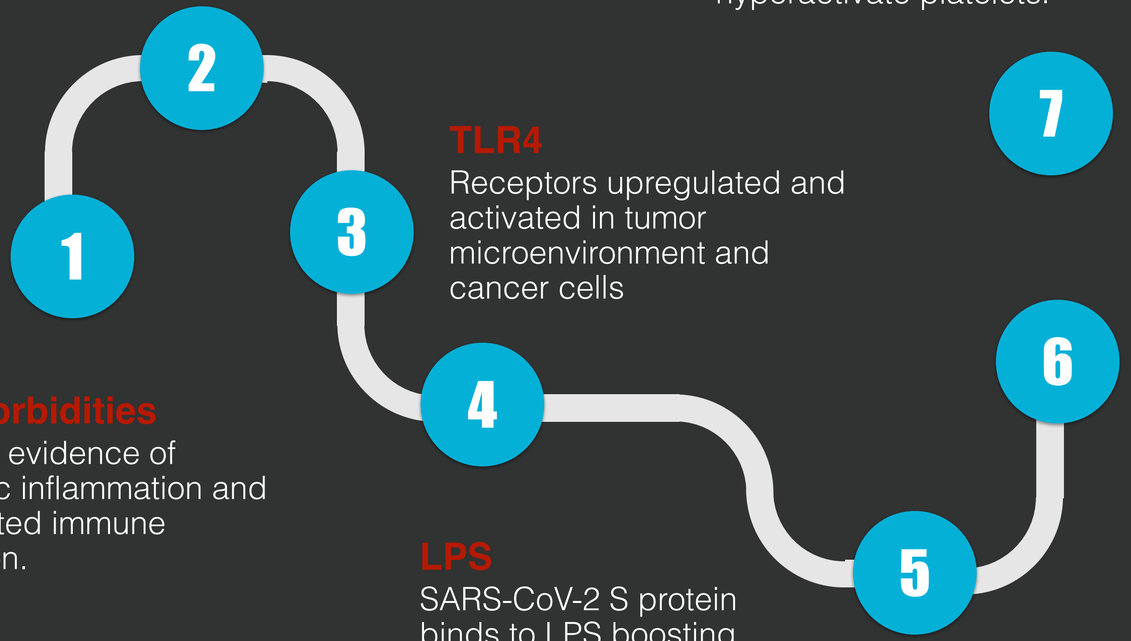

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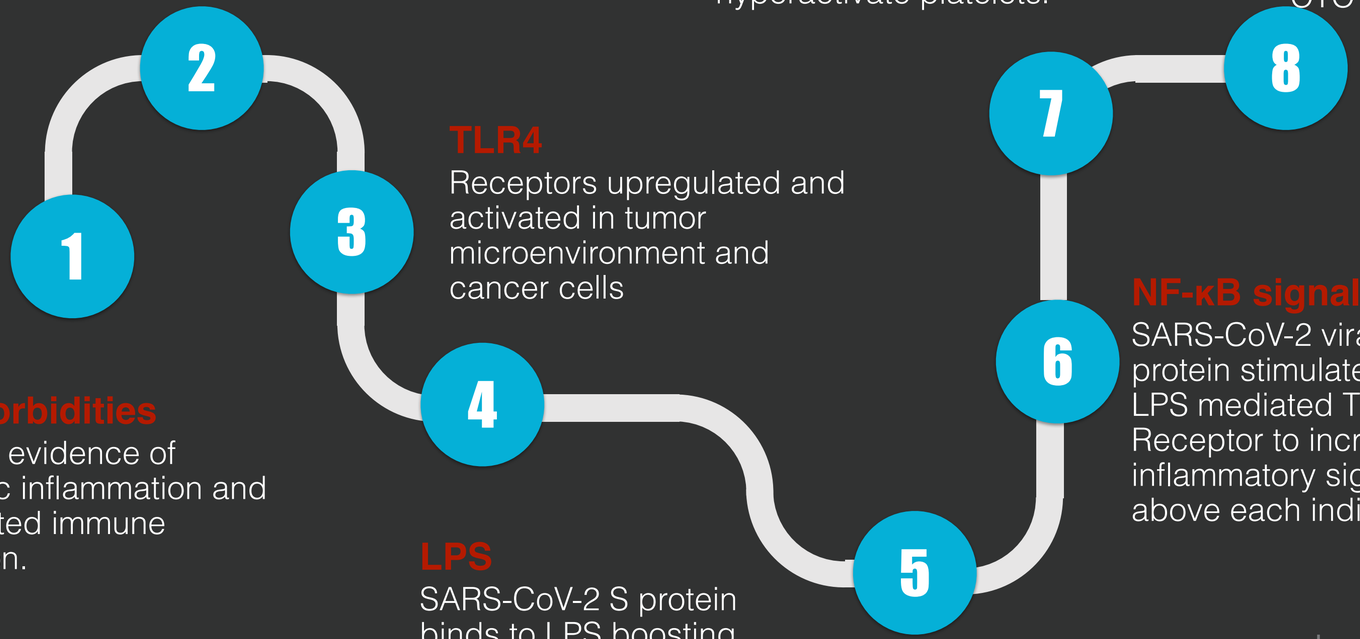

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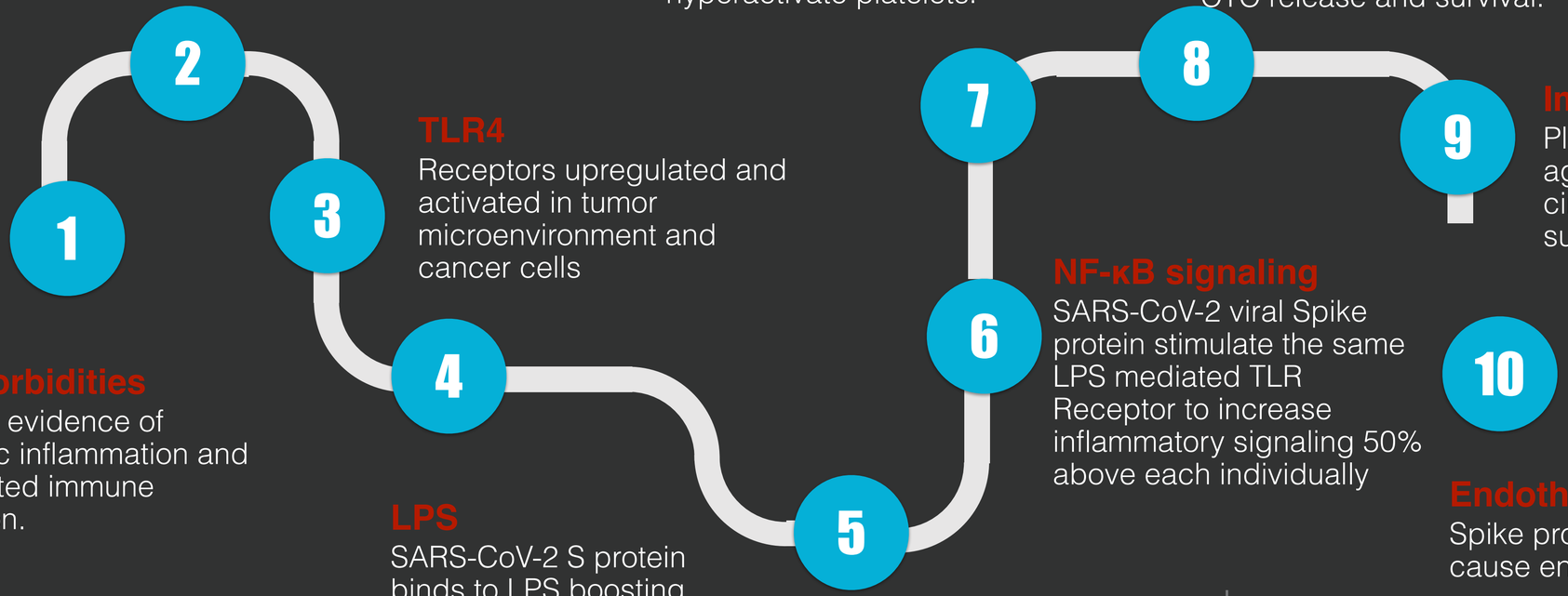

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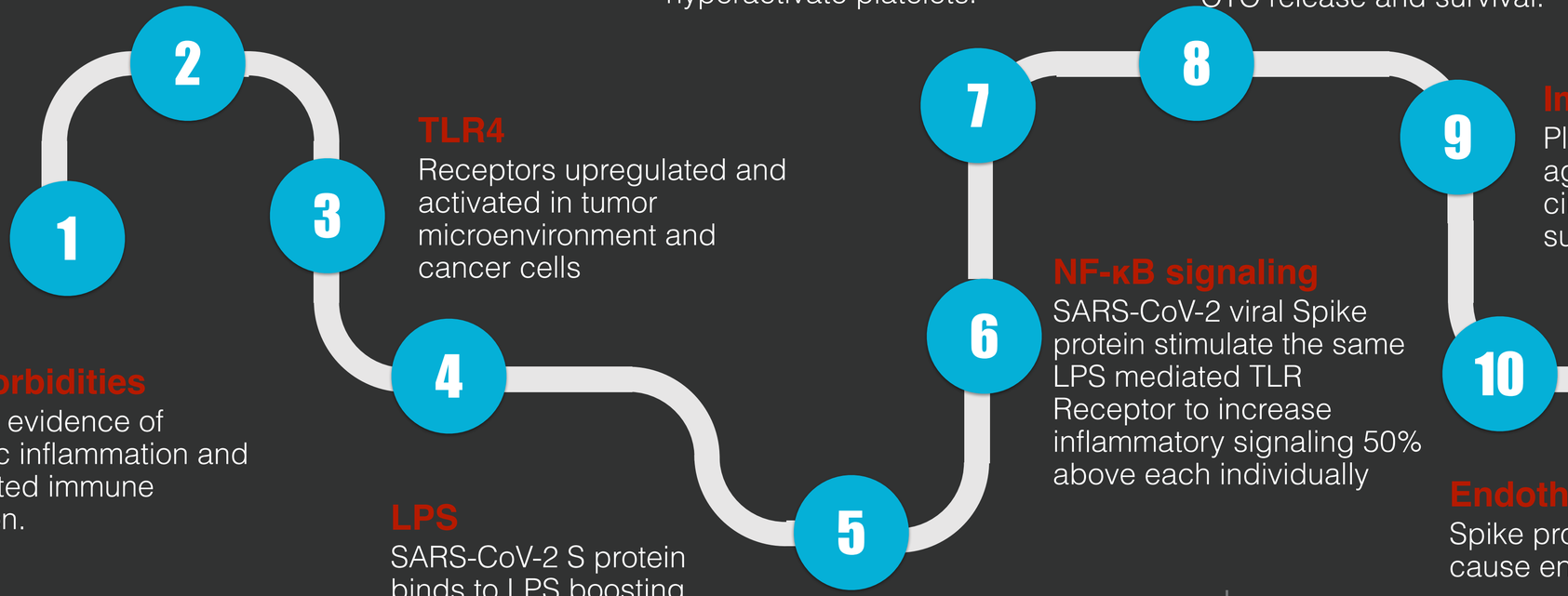


Comorbidities
Visible evidence of chronic inflammation and disrupted immune function.

Toxins
Spike proteins is, in fact, a toxin, or a toxicant depending on the source of origin.

TLR4
Receptors upregulated and activated in tumor microenvironment and cancer cells

LPS
SARS-CoV-2 S protein binds to LPS boosting inflammatory response.

Receptors
ACE2 and integrin αvβ3 receptors serve as the gateway to the cell's internal machinery via the spike protein.

Platelets
Spike proteins hyperactivate platelets.

NF-κB signaling
SARS-CoV-2 viral Spike protein stimulate the same LPS mediated TLR Receptor to increase inflammatory signaling 50% above each individually

Circulating Tumor Cells (CTC)
Increased inflammatory signaling and immune escape increase CTC release and survival.

Immune Escape
Platelet-Cancer cell aggregates evade circulating immune surveillance.

Endothelium damage
Spike proteins directly cause endothelial damage.

Micrometastasis

Metastatic Map

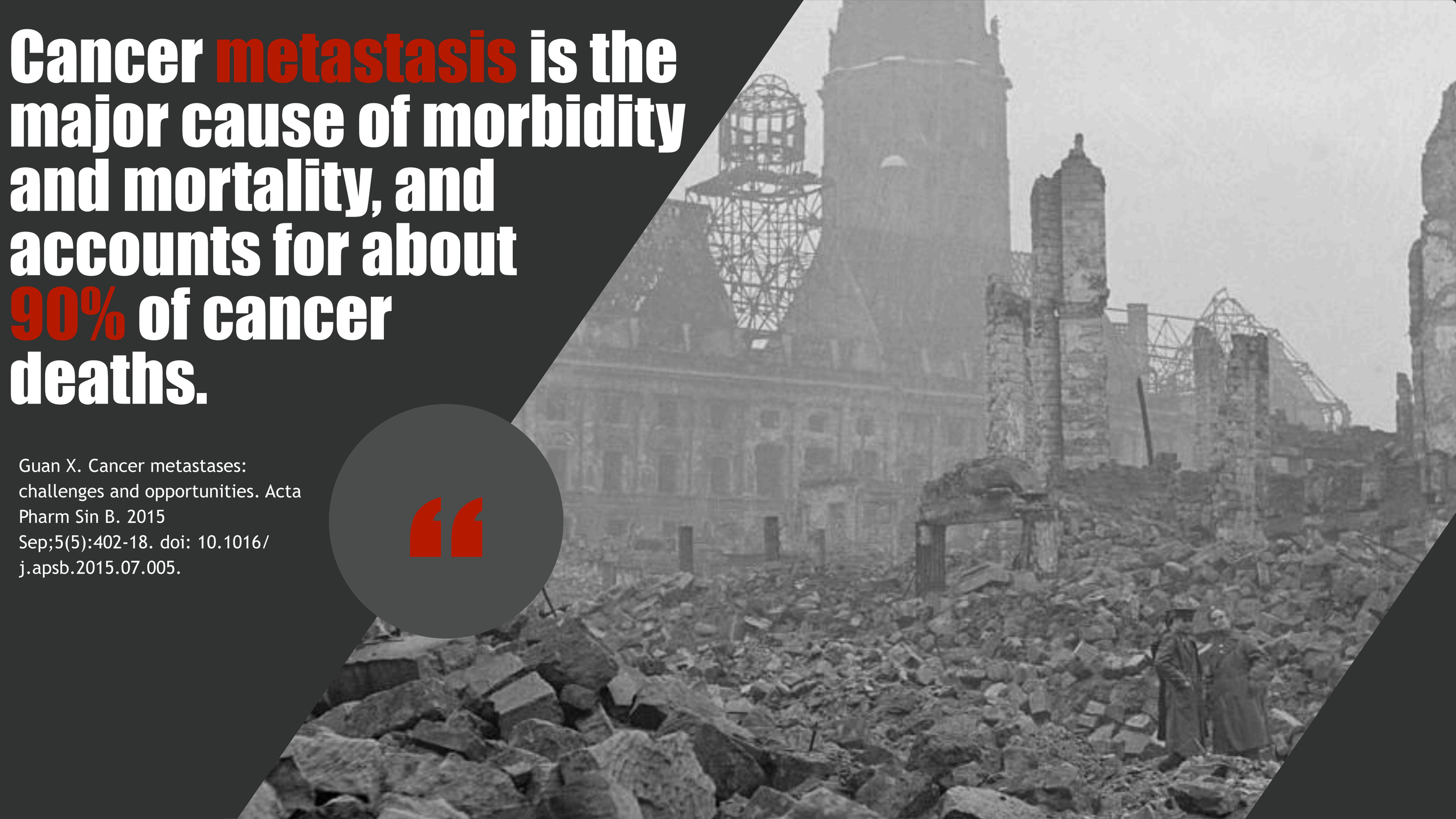
90% of morbidity and mortality associated with cancer is when cancer spreads to distant organ sites—metastasis.

"Compared to the SARS-CoV-2 WT, the Gamma variant induced a **stronger NF-κB activation**, leading to a more **aggressive** cancerous phenotype. These results suggest cancer patients with COVID-19 Gamma variant infection may experience a **strong** potential of cancer **metastasis** or **recurrence**...SARS-CoV-2 **activates** NF-κB and, in turn, **triggers** the **pro-survival** function for cancer **progression**"

—Huang HC, Liao CC, Wang SH et al. ***Hyperglycosylated spike of SARS-CoV-2 gamma variant induces breast cancer metastasis.***

Cancer metastasis is the major cause of morbidity and mortality, and accounts for about 90% of cancer deaths.

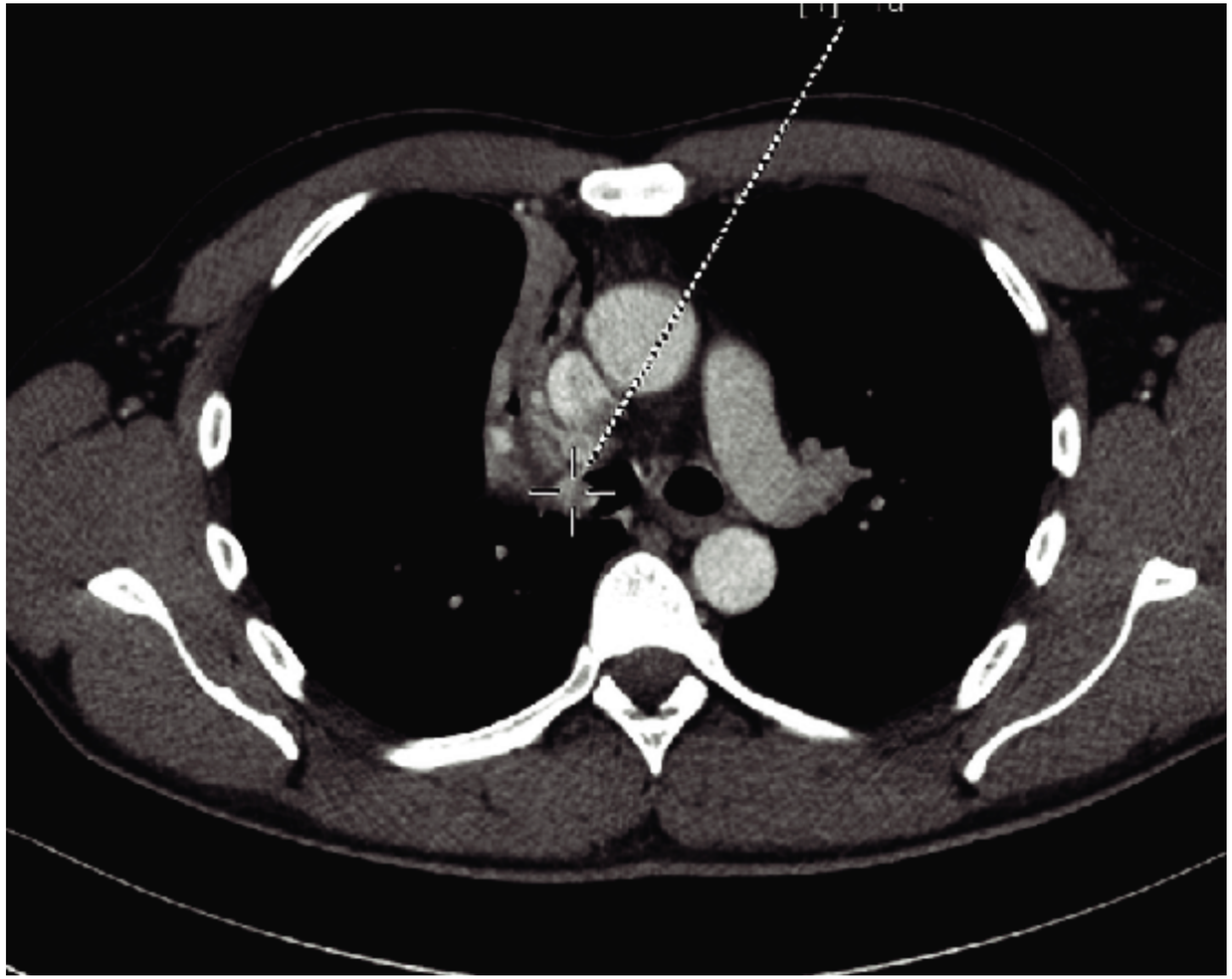
Guan X. Cancer metastases: challenges and opportunities. Acta Pharm Sin B. 2015 Sep;5(5):402-18. doi: 10.1016/j.apsb.2015.07.005.



RS

Case study #3

- 66 y/o with Stage IV recurrent Colorectal cancer in 2020 (originally diagnosed in 2012)
- Radiation 2019 and 2021
- MTD chemotherapy for 2.5 years
- Widespread Lung metastasis
- COVID vaccination #1 (1.'21), #2 (2.'21)



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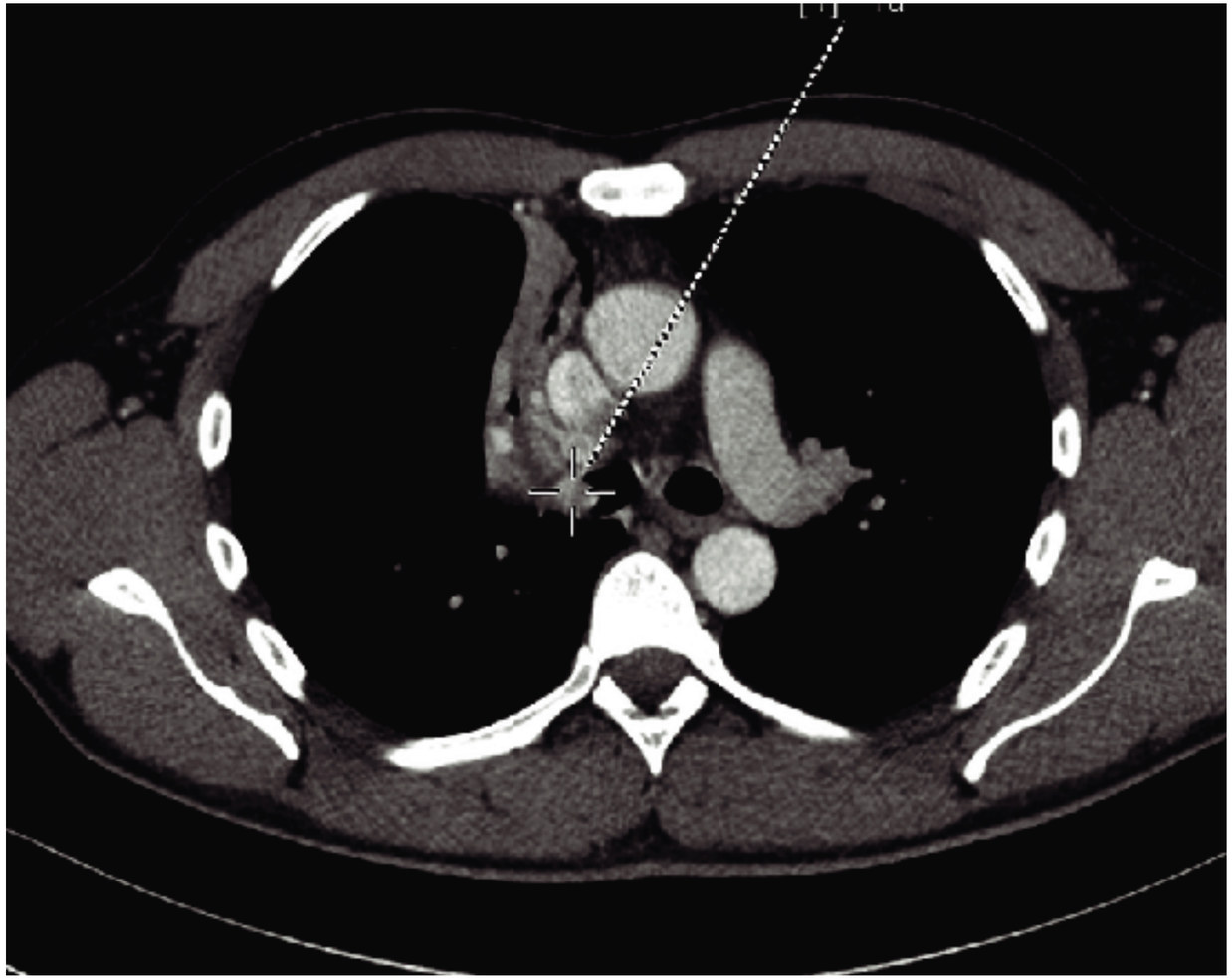


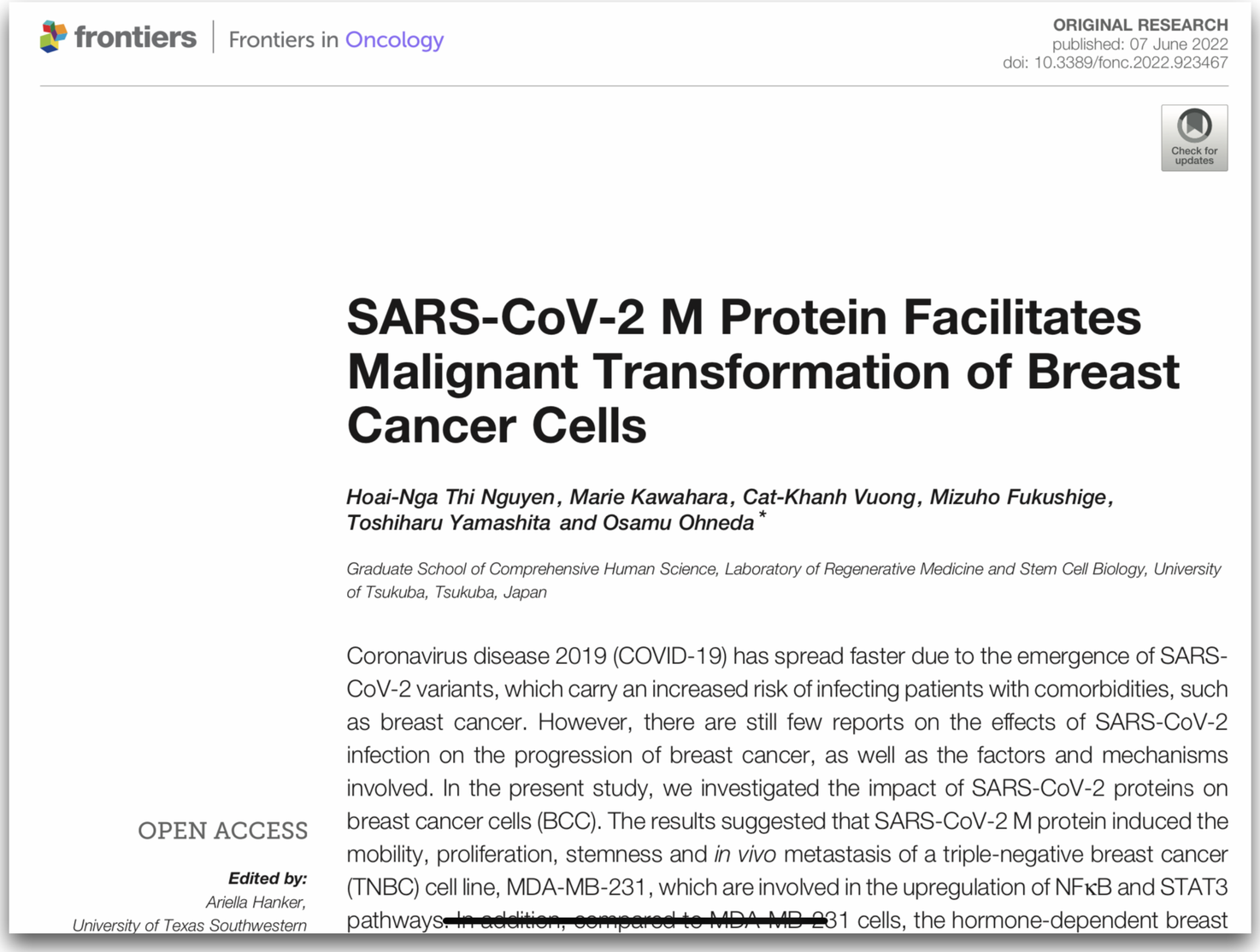
Mind

Blowing!

M Protein

Malignant Transformation

- ACE2 upregulation
- Proliferation
- Migration
- Epithelial to Mesenchymal transition (Vimentin)
- Inflammatory cytokine expression (cytokine storm)
- Tumor progression
- Metastasis
- Stemness



frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 07 June 2022
doi: 10.3389/fonc.2022.923467

Check for updates

SARS-CoV-2 M Protein Facilitates Malignant Transformation of Breast Cancer Cells

Hoai-Nga Thi Nguyen, Marie Kawahara, Cat-Khanh Vuong, Mizuho Fukushige, Toshiharu Yamashita and Osamu Ohneda *

Graduate School of Comprehensive Human Science, Laboratory of Regenerative Medicine and Stem Cell Biology, University of Tsukuba, Tsukuba, Japan

Coronavirus disease 2019 (COVID-19) has spread faster due to the emergence of SARS-CoV-2 variants, which carry an increased risk of infecting patients with comorbidities, such as breast cancer. However, there are still few reports on the effects of SARS-CoV-2 infection on the progression of breast cancer, as well as the factors and mechanisms involved. In the present study, we investigated the impact of SARS-CoV-2 proteins on breast cancer cells (BCC). The results suggested that SARS-CoV-2 M protein induced the mobility, proliferation, stemness and *in vivo* metastasis of a triple-negative breast cancer (TNBC) cell line, MDA-MB-231, which are involved in the upregulation of NFκB and STAT3 pathways. In addition, compared to MDA-MB-231 cells, the hormone-dependent breast

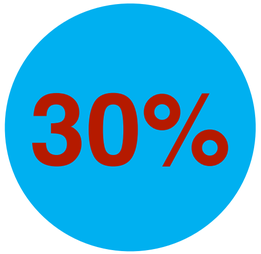
OPEN ACCESS

Edited by:
Ariella Hanker,
University of Texas Southwestern

Nguyen HT, Kawahara M, Vuong CK, Fukushige M, Yamashita T, Ohneda O. SARS-CoV-2 M Protein Facilitates Malignant Transformation of Breast Cancer Cells. Front Oncol. 2022 Jun 7;12:923467. doi: 10.3389/fonc.2022.923467.


LONG COVID
LONG-HAULERS
ONGOING SYMPTOMS
PERSISTENT SYMPTOMS
COVID-19
CORONAVIRUS
FATIGUE
COUGH
SEQUELAE
CHEST TIGHTNESS
NEUROPATHY
BREATHLESSNESS
SHORTNESS OF BREATH
INSOMNIA
CHEST PAIN
LACK TASTE
LACK SMELL
BODY ACHE
MUSCLE ACHE
LONG-TERM
POST-COVID-19 SYNDROME
HEADACHE
RASH
FOCUS
HAIR LOSS
DIFFICULTY BREATHING
NAUSEA
LOW FEVER
CONCENTRATION
EARACHE
TINNITUS
SORE THROAT
RUNNY NOSE
DEPRESSION
MEMORY ISSUES
DELIRIUM
BRAIN FOG
JOINT PAIN
CONGESTION
TREMORS
SHAKING
CHILLS
DIZZINESS
ANXIETY
ABDOMINAL PAIN
HEART PALPITATIONS
NUMBNESS
BLURRY VISION
BACK PAIN
SLEEP DISTURBANCE
NERVE DIFFICULTIES
HEAT INTOLERANCE
COGNITIVE IMPAIRMENT
REDUCED APPETITE
PERMANENT DAMAGE
PSYCHIATRIC SYMPTOMS
PERIPHERAL NEUROPATHY
PINS AND NEEDLES

- chronic fatigue
- brain fog
- sleep difficulties
- joint pains
- pharyngitis
- muscle aches/pains
- headaches
- fevers
- gastrointestinal upset
- skin rashes



What is long-Covid?

“a syndrome characterized by the persistence or development of symptoms attributed to COVID-19 more than 12 weeks after initial infection.”

—StatPearls, 2023

- **Heart and Kidney**
- **Respiratory, sleep, and anxiety**
- **Musculoskeletal and nervous system**
- **Digestive and respiratory**

Definition?

“newly incident diagnoses 30–180 days after a documented SARS-CoV-2 infection”

—Zhang H, Zang C, Xu Z et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes

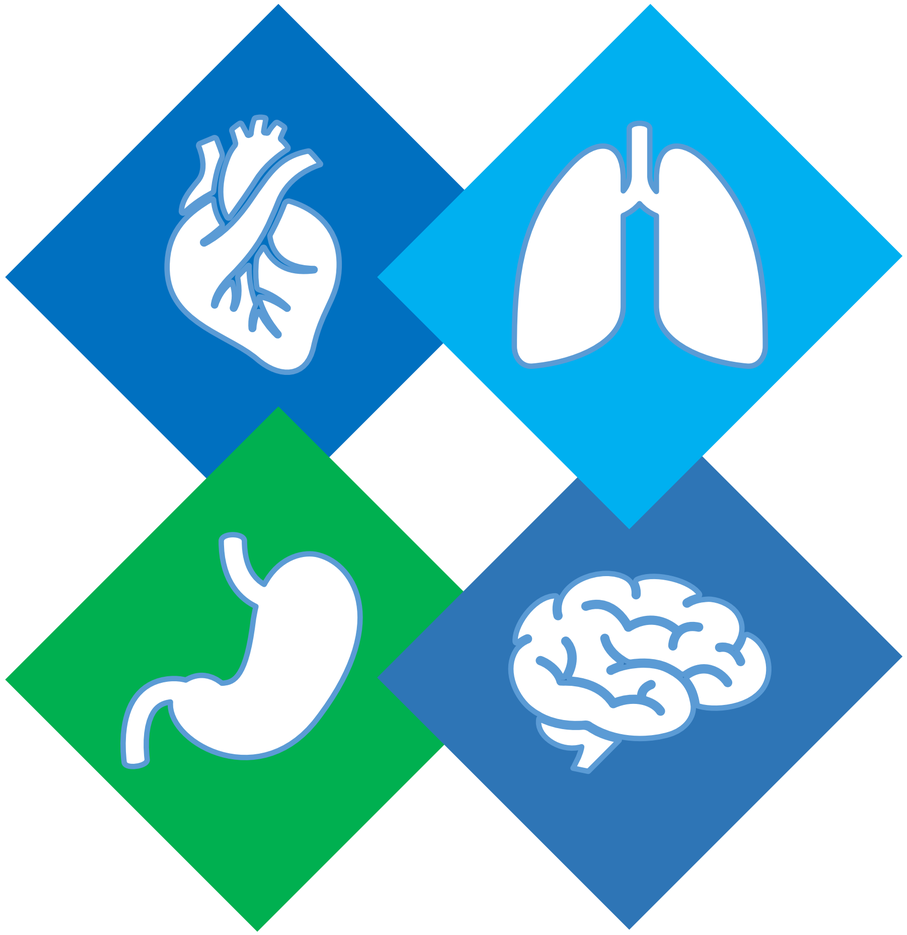
2022

Long-COVID

Sub-phenotypes

Category 1

cardiac and circulatory conditions, renal failure, anemia and fluid and electrolyte disorders.



Category 2

respiratory conditions, sleep disorders, anxiety…headache and chest pain.

Category 4

digestive and respiratory symptoms. This last category had the lowest severity ranking of the four.

Category 3

musculoskeletal pain, headaches and sleep-wake disorders.

It is evident that the symptoms of long Covid follow the the pre-existing trail of chronic inflammation, immune disruption, and organ system disruption. It appears that long Covid merely exacerbates that which pre-existed.

What are the proposed cause(s) of long-Covid?

Is it merely following pre-existing pathways of dysfunction and inflammation, a path previously traveled? Or, is it something else. Or, is it a combination?

4

- chronic viral infection
- Inflammation
- NETosis
- Viral reactivation
- Spike proteins

What are the proposed cause(s) of long-Covid?

Is it merely following pre-existing pathways of dysfunction and inflammation, a path previously traveled? Or, is it something else. Or, is it a combination?

- Viral reactivation
- Reactivation of oncogenic viruses
- Reactivation/Effects of other pathogens
- Increased lifetime viral load
- Activation of shared molecular mechanisms between SARS-CoV-2 and cancer
- Manipulation of oncogenic signaling pathways
- Inflammation
- Immunomodulation (T cell and NK cell exhaustion)
- Persistent spike protein reservoirs
- Persistent SARS-CoV-2 virus

What is is the connection between long-Covid and cancer?

In many ways, it is the same connection that exists between the spike protein and cancer, whether from **injection** or **infection**.

- Herpes simplex virus type 1 (oral herpes, such as cold sores)
- Herpes simplex virus type 2 (genital herpes)
- Varicella-zoster virus
- Epstein-Barr virus
- Cytomegalovirus
- Human herpesvirus 6
- Kaposi sarcoma-associated herpesvirus
- John Cunningham (JC) virus
- BK virus
- Parvovirus B19
- Adenovirus
- HIV

Viral Reactivation

Triggers: Stress, other infections, inflammation

research points to the possibility that long Covid is the result of reactivation of latent viruses. A latent virus is a previously infectious virus that has gone into dormancy or latency.

Viral Reactivation

"*Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus* ***Reactivation***"

67% of individuals "were **positive for EBV reactivation** based on positive titers for EBV early antigen-diffuse (EA-D) IgG or EBV viral capsid antigen (VCA) IgM."

"These findings suggest that many long COVID symptoms may not be a direct result of the SARS-CoV-2 virus **but** may be the result of COVID-19 inflammation-induced EBV **reactivation**."

"Lensen R, Netea MG, Rosendaal FR. Hepatitis C Virus ***Reactivation*** *Following COVID-19 Vaccination – A Case Report*"

"…**reactivation of hepatitis C virus** (day #3) after vaccination with the Pfizer–BioNTech COVID-19 vaccine…a strong increase in HCV load occurred a few days after vaccination."

"One possibility, as in the case of Kaposi sarcoma-associated herpesvirus, is that SARS-CoV-2 encoded proteins may cause **reactivation** of the hepatitis C virus. Alternatively, an indirect mechanism through **induction** of inflammation and cytokines, that would subsequently influence viral replication, is also possible."

Oncogenic viruses

Epstein–Barr virus (EBV)
Causative agent of mononucleosis

Cytomegalovirus (CMV)
Common “childhood virus” type of Herpesvirus (type 5)

hepatitis B virus (HBV)
A hepadnaviurs that infects the liver, and causes liver inflammation—hepatitis.

hepatitis C virus (HCV)
Infects the liver and causes severe liver inflammation; infections can be acute and chronic—hepatitis.

Carcinogenic causative agent

Accumulating factors

Additional factors

human T-lymphotropic virus 1 (HTLV-1)
Similar to HIV, can cause life-long infections in humans; first oncogenic virus discovered (1977).

human papillomaviruses (HPVs)
Common viral infection with over 100 varieties currently known; most common sexually transmitted infection.

Kaposi sarcoma-associated herpesvirus (KSHV)
A human herpesvirus-8 (HHV-8) present in all epidemiological forms of Kaposi Sarcoma.

Merkel cell polyomavirus (MCPyV)
Common infection in human population with carcinogenic link to Merkel Cell Carcinoma (MCC)

Reactivation

Of oncogenic viruses

15-20% of all cancer types, worldwide,

are caused by viruses.

1. Epstein-Barr virus (EBV)
2. Cytomegalovirus (CMV)
3. hepatitis B virus (HBV)
4. human T-lymphotropic virus 1 (HTLV-1)

pathogens

MDPI

Article

Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation

Jeffrey E. Gold [1,*], Ramazan A. Okyay [2], Warren E. Licht [3] and David J. Hurley [4]

[1] World Organization, Watkinsville, GA 30677, USA
[2] Department of Public Health, Kahramanmaraş Sütçü İmam University, Kahramanmaraş 46040, Turkey; razim01@gmail.com
[3] Warren Alpert Medical School of Brown University, Providence, RI 02903, USA; warren.licht@brownphysicians.org
[4] College of Veterinary Medicine, University of Georgia, Athens, GA 30602, USA; djhurley@uga.edu
* Correspondence: jeff_gold@world.org

Abstract: Coronavirus disease 2019 (COVID-19) patients sometimes experience long-term symptoms following resolution of acute disease, including fatigue, brain fog, and rashes. Collectively these have become known as long COVID. Our aim was to first determine long COVID prevalence in 185 randomly surveyed COVID-19 patients and, subsequently, to determine if there was an association between occurrence of long COVID symptoms and reactivation of Epstein–Barr virus (EBV) in 68 COVID-19 patients recruited from those surveyed. We found the prevalence of long COVID symptoms to be 30.3% (56/185), which included 4 initially asymptomatic COVID-19 patients who later developed long COVID symptoms. Next, we found that 66.7% (20/30) of long COVID subjects

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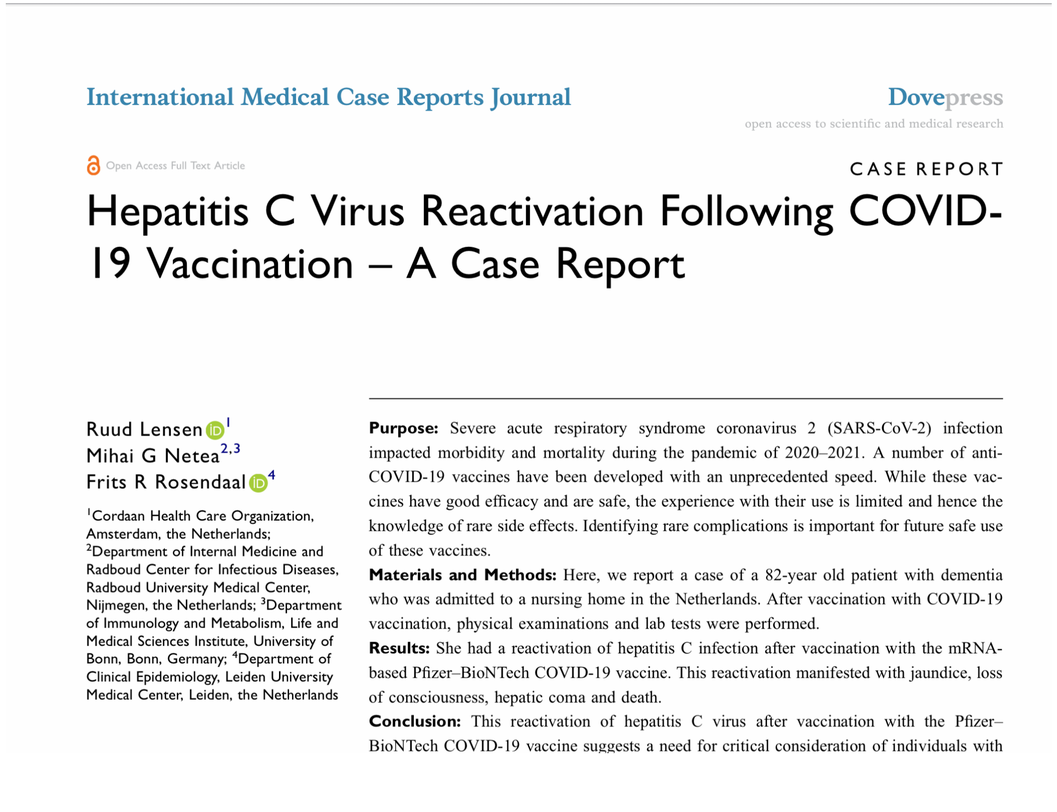
4. Merkel cell polyomavirus (MCPyV)



International Medical Case Reports Journal

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CASE REPORT

Hepatitis C Virus Reactivation Following COVID-19 Vaccination – A Case Report

Ruud Lensen[1]
Mihai G Netea[2,3]
Frits R Rosendaal[4]

[1]Cordaan Health Care Organization, Amsterdam, the Netherlands; [2]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands; [3]Department of Immunology and Metabolism, Life and Medical Sciences Institute, University of Bonn, Bonn, Germany; [4]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

Purpose: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection impacted morbidity and mortality during the pandemic of 2020–2021. A number of anti-COVID-19 vaccines have been developed with an unprecedented speed. While these vaccines have good efficacy and are safe, the experience with their use is limited and hence the knowledge of rare side effects. Identifying rare complications is important for future safe use of these vaccines.

Materials and Methods: Here, we report a case of a 82-year old patient with dementia who was admitted to a nursing home in the Netherlands. After vaccination with COVID-19 vaccination, physical examinations and lab tests were performed.

Results: She had a reactivation of hepatitis C infection after vaccination with the mRNA-based Pfizer–BioNTech COVID-19 vaccine. This reactivation manifested with jaundice, loss of consciousness, hepatic coma and death.

Conclusion: This reactivation of hepatitis C virus after vaccination with the Pfizer–BioNTech COVID-19 vaccine suggests a need for critical consideration of individuals with

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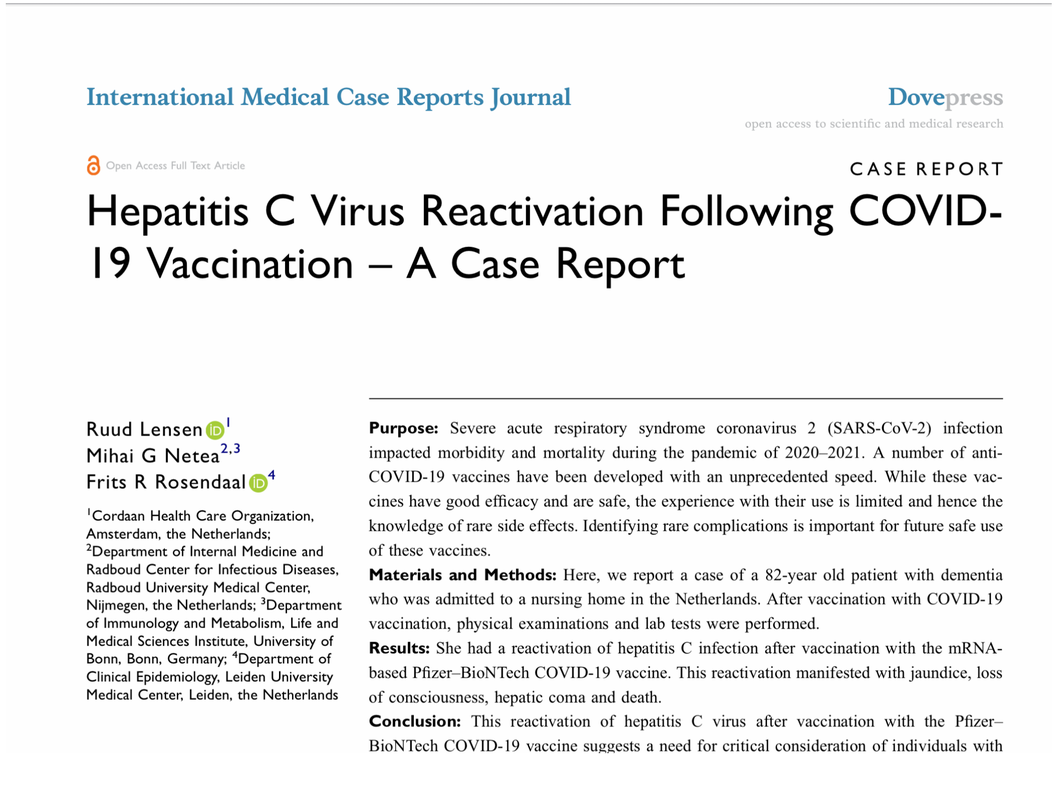

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2. Bacteria (Helicobacter pylori)
3. Bacteria (microbiome)
4. Fungal

J Parasit Dis (July-Sept 2019) 43(3):464–471
https://doi.org/10.1007/s12639-019-01111-9

ORIGINAL ARTICLE

J P D

Toxoplasma gondii in cancer patients receiving chemotherapy: seroprevalence and interferon gamma level

Mona Ibrahim Ali[1] · Wegdan Mohamed Abd El Wahab[1] · Doaa Ahmed Hamdy[1] · Ahmed Hassan[2]

Received: 2 February 2019 / Accepted: 26 March 2019 / Published online: 30 March 2019

Abstract *Toxoplasma gondii* is an opportunistic parasite causing life-threatening diseases in immune-compromised patients. The purpose of the study is to determine the seroprevalence of *Toxoplasma gondii* in chemotherapy receiving cancer patients in relation to different types of malignancies, and to estimate the level of interferon gamma in *Toxoplasma* seropositive and seronegative cancer patients and healthy controls. Anti-*Toxoplasma* IgG and IgM antibodies, and interferon gamma were analyzed in 120 [illegible] patients [illegible] (60 [illegible]). However, it was highly elevated in *Toxoplasma* seropositive (76 pg/ml) than seronegative (44.5 pg/ml) cases with statistical significance ($p < 0.001$). *T. gondii* infection remains a major threat to cancer patients and still needs proper screening, diagnosis and treatment.

Keywords *Toxoplasma gondii* · Seroprevalence · Cancer patients · Interferon gamma

Reactivation

Or effects of other pathogens

"Significant changes in **gut microbiota** and microbiota have been demonstrated in early studies in patients with COVID-19… SARS-CoV-2-associated gut microbiome alteration could be a new **contributor to colorectal cancer pathogenesis**…"

1. Parasitic (Toxoplasmosis gondii)
2. Bacteria (Helicobacter pylori)
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4. Fungal

Pathology - Research and Practice 239 (2022) 154131

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

SARS-CoV-2-associated gut microbiome alteration; A new contributor to colorectal cancer pathogenesis

Shahrooz Amin Mozaffari [a], Ali Salehi [b], Elnaz Mousavi [c], Burhan Abdullah Zaman [d], Ali Eslambol Nassaj [e], Farnoosh Ebrahimzadeh [f], Hadi Nasiri [a], Zahra Valedkarimi [a], Ali Adili [g,h], Ghazaleh Asemani [a], Morteza Akbari [a,i,*]

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[e] Department of Endodontics, School of Dentistry, Kerman University of Medical Sciences, Kerman, Islamic Republic of Iran
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[g] Senior Adult Oncology Department, Moffitt Cancer Center, University of South Florida, Tampa, USA
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[i] Department of Medical Biotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Islamic Republic of Iran

ARTICLE INFO

Keywords:
COVID-19

ABSTRACT

The emergence of a novel coronavirus, COVID-19, in December 2019 led to a global pandemic with more than 170 million confirmed infections and more than 6 million deaths (by July 2022). Studies have shown that

Reactivation

Or effects of other pathogens

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Research

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Journal of Emergency and Internal Medicine
ISSN 2576-3938

2022
Vol.6 No.5:33

SARS-CoV-2 and Helicobacter Pylori: Can they Become Co-Pathogens?

Giovanni Gasbarrini[1*], Fabrizio Termite[2], Stefano Simeoni[3] and Fiorenza Bonvicini[4]

[1]Department of Internal Medicine, Catholic University, Roma, Italy

[2]Department of Internal Medicine and Gastroenterology, Catholic University, Roma, Italy

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Received date: August 13, 2022, Manuscript No. IPJEIM-22-14328; **Editor assigned date:** August 15, 2022, PreQC No. IPJEIM-22-14328 (PQ); **Reviewed date:** August 29, 2022, QC No. IPJEIM-22-14328; **Revised date:** September 09, 2022, Manuscript No. IPJEIM-22-14328 (R); **Published date:** September 21, 2022, DOI: 10.36648/2576-3938.6.5.33.

Citation: Gasbarrini G, Termite F, Simeoni S, Bonvicini F (2022) SARS-CoV-2 and Helicobacter Pylori: Can they Become Co-Pathogens?. Intern Emerg Med Vol.6 No.5: 33.

Abstract

Objective: SARS-CoV-2 binds to ACE (Angiotensin Converting Enzyme)-2 receptors that are expressed not only in the respiratory tract but also in the gastrointestinal tract. During Pandemia we treated more outpatients for Helicobacter

Keywords: Helicobacter Pylori (HP); COVID-19; SARS-CoV-2; Pandemic; Co-Pathogenicity; Secondary Infections; ACE-2 receptor.

Introduction

Reactivation

Or effects of other pathogens

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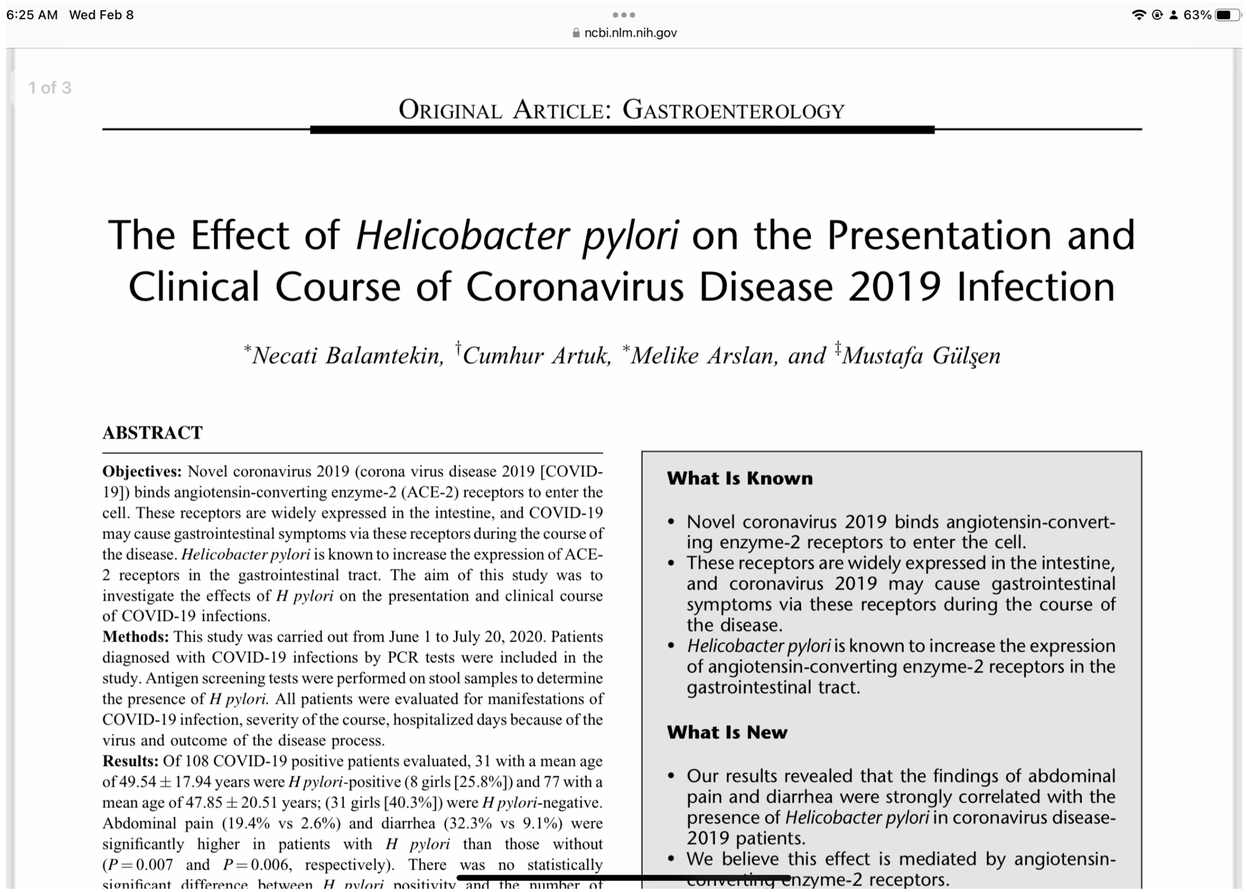

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Review Article | Published: 01 June 2022

Human Fungal Infection, Immune Response, and Clinical Challenge—a Perspective During COVID-19 Pandemic

Kumar Vishven Naveen, Kandasamy Saravanakumar, Anbazhagan Sathiyaseelan, Davoodbasha MubarakAli & Myeong-Hyeon Wang

Applied Biochemistry and Biotechnology **194**, 4244–4257 (2022) | Cite this article

1761 Accesses | **2** Citations | **1** Altmetric | Metrics

Abstract

Fungi are a small but important part of the human microbiota and several fungi are familiar to the immune system, yet certain can cause infections in immunocompromised hosts and referred as opportunistic pathogens. The fungal

Reactivation

Or effects of other pathogens

"Significant changes in **gut microbiota** and microbiota have been demonstrated in early studies in patients with COVID-19… SARS-CoV-2-associated gut microbiome alteration could be a new **contributor to colorectal cancer pathogenesis**…"

Increased

Lifetime viral load

The **cumulative** infectious exposure across a lifespan is likely where the more **significant** pro-carcinogenic, immunologic impact can be found

1. Acute infection
2. Chronic inflammation
3. Immunosuppression potentiation
4. Immune escape
5. Impaired cancer surveillance
6. Increased metastatic potential

Lian *et al. J Hematol Oncol* (2020) 13:151
https://doi.org/10.1186/s13045-020-00986-z

Journal of Hematology & Oncology

REVIEW Open Access

Immunosenescence: a key player in cancer development

Jingyao Lian[1,2†], Ying Yue[1,2,3†], Weina Yu[1,2†] and Yi Zhang[1,2*]

Abstract

Immunosenescence is a process of immune dysfunction that occurs with age and includes remodeling of lymphoid organs, leading to changes in the immune function of the elderly, which is closely related to the development of infections, autoimmune diseases, and malignant tumors. T cell–output decline is an important feature of immunosenescence as well as the production of senescence-associated secretory phenotype, increased glycolysis, and reactive oxygen species. Senescent T cells exhibit abnormal phenotypes, including downregulation of CD27, CD28, and upregulation of CD57, killer cell lectin-like receptor subfamily G, Tim-3, Tight, and cytotoxic T-lymphocyte-associated protein 4, which are tightly related to malignant tumors. The role of immunosenescence in tumors is sophisticated: the many factors involved include cAMP, glucose competition, and oncogenic stress in the tumor microenvironment, which can induce the senescence of T cells, macrophages, natural killer cells, and dendritic cells. Accordingly, these senescent immune cells could also affect tumor progression. In addition, the effect of immunosenescence on the response to immune checkpoint blocking antibody therapy so far is ambiguous due to the low participation of elderly cancer patients in clinical trials. Furthermore, many other senescence-related interventions could be possible with genetic and pharmacological methods, including mTOR inhibition, interleukin-7 recombination, and NAD^+ activation. Overall,

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ELSEVIER

Social Science & Medicine

Volume 52, Issue 8, April 2001, Pages 1269-1284

Does childhood health affect chronic morbidity in later life?

Debra L Blackwell [a], Mark D Hayward [b], Eileen M Crimmins [c]

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Leonardi *et al. Immunity & Ageing* (2018) 15:1
DOI 10.1186/s12979-017-0112-5

Immunity & Ageing

REVIEW Open Access

Ageing: from inflammation to cancer

Giulia C. Leonardi[1†], Giulia Accardi[2†], Roberto Monastero[3], Ferdinando Nicoletti[1] and Massimo Libra[1*]

Abstract

Ageing is the major risk factor for cancer development. Hallmark of the ageing process is represented by inflammaging, which is a chronic and systemic low-grade inflammatory process. Inflammation is also a hallmark of cancer and is widely recognized to influence all cancer stages from cell transformation to metastasis. Therefore, inflammaging may represent the biological phenomena able to couple ageing process with cancer development. Here we review the molecular and cellular pathway involved in age-related chronic inflammation along with its potential triggers and their connection with cancer development.

Keywords: Ageing, Cancer, DAMPs, Inflammation, Microbiota, MiRna, Obesity, Senescence

Background

Inflammation, inflammaging and cancer

Ageing is a nearly universal biological process characterized, in multicellular organisms, by the progressive loss of cells functions and tissues renewal due to complex, heterogeneous and dynamic mechanisms and affected by several genetic, epigenetic, environmental and fortuitous factors [1, interleukins such as IL-6, IL-1 and Tumor Necrosi Factor(TNF)-α and inflammatory markers, such as CRP [6]. This results from the activation of signalling networks critical to inflammation, such as those regulated by the Nuclear Factor (NF)-kB transcription factor, along with a variety of different sources of the inflammatory stimuli triggering and sustaining inflammaging, such as senescent cells, the meta-

- Hypoxia
- Hyperinflammation
- Oxidative stress
- Immune system suppression
- Altered/manipulated signaling pathways

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Activation

of shared molecular mechanisms between SARS-CoV-2 and cancer

SARS-CoV-2 shares common molecular pathways with cancer. As a result, SARS-Cov-2 **activates** the **common, shared** molecular pathways.

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Activation

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Manipulation

of oncogenic signaling pathways

The effects of infection on pathways relevant to cancer could affect **cell proliferation**, **development**, **survival**, and **metastasis**, favoring DNA degradation, preventing the repair of damaging events, and impeding the translation of RNA into functional proteins, and could lead to a more rapid disease progression

- Pi3K-AKT-mTor signaling pathway
- MAPK signaling pathway
- Notch signaling pathway
- WNT/β-catenin signaling pathway
- Galectin-3
- Platelet hyperactivation

The network of SARS-CoV-2—cancer molecular interactions and pathways

Pau Erola, Richard M. Martin, Tom R. Gaunt

doi: https://doi.org/10.1101/2022.04.04.487020

Abstract

Background Relatively little is known about the long-term impacts of SARS-CoV-2 biology, including whether it increases the risk of cancer. This study aims to identify the molecular interactions between COVID-19

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Manipulation

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SARS-CoV-2, and other oncogenic viruses,

co-opt, **adulterate**, **manipulate**, and

propagate oncogenic signaling pathways.

- NF-κB signaling pathway
- DNA damage response (DDR)
- P53 tumor suppressor down regulation
- ACE2 activated RAS imbalance
- integrin αVβ3

f 5

Transfusion and Apheresis Science 61 (2022) 103488

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SARS-CoV-2 and cancer: the intriguing and informative cross-talk

Hadi Goubran [a], Julie Stakiw [a], Jerard Seghatchian [b], Gaafar Ragab [c,d], Thierry Burnouf [e,f,*]

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ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Cancer
Cross-talk

ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus has significantly disrupted and burdened the diagnostic workup and delivery of care, including transfusion, to cancer patients across the globe. Furthermore, cancer patients suffering from solid tumors or hematologic malignancies were more prone to the infection and had higher morbidity and mortality than the rest of the population. Major signaling pathways have been identified at the intersection of SARS-CoV-2 and cancer cells, often leading to tumor progression or alteration of the tumor response to therapy. The reactivation of oncogenic viruses has also been alluded to in the context and following COVID-19. Paradoxically, certain tumors responded better following the profound infection-induced immune modulation. Unveiling the mechanisms of the virus-tumor cell interactions will lead to a better understanding of the pathophysiology of both cancer progression and virus propagation. It would be challenging to monitor, through the different cancer registries, retrospectively, the response of patients who have been previously exposed to the virus in contrast to those who have not contracted the infection

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- Nuclear factor kappa B (NF-κB)
- Interleukin-6 (IL-6)
- Toll-Like Receptor 4 (TLR4)
- NETosis

Research article

SARS-CoV-2 spike protein S1 subunit induces pro-inflammatory responses via toll-like receptor 4 signaling in murine and human macrophages

Ken Shirato *, Takako Kizaki

Department of Molecular Predictive Medicine and Sport Science, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan

ARTICLE INFO

Keywords:
SARS-CoV-2
Spike protein
S1 subunit
Toll-like receptor 4
Inflammation
Macrophage

ABSTRACT

Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome co navirus 2 (SARS-CoV-2), has now spread globally. Some patients develop severe complications including multi organ failure. It has been suggested that excessive inflammation associated with the disease plays major role the severity and mortality of COVID-19. To elucidate the inflammatory mechanisms involved in COVID-19, examined the effects of SARS-CoV-2 spike protein S1 subunit (hereafter S1) on the pro-inflammatory responses murine and human macrophages. Murine peritoneal exudate macrophages produced pro-inflammatory mediat in response to S1 exposure. Exposure to S1 also activated nuclear factor-κB (NF-κB) and c-Jun N-terminal kina (JNK) signaling pathways. Pro-inflammatory cytokine induction by S1 was suppressed by selective inhibitors NF-κB and JNK pathways. Treatment of murine peritoneal exudate macrophages and human THP-1 cell-deriv macrophages with a toll-like receptor 4 (TLR4) antagonist attenuated pro-inflammatory cytokine induction a the activation of intracellular signaling by S1 and lipopolysaccharide. Similar results were obtained in expe ments using TLR4 siRNA-transfected murine RAW264.7 macrophages. In contrast, TLR2 neutralizing antibod could not abrogate the S1-induced pro-inflammatory cytokine induction in either RAW264.7 or THP-1 c derived macrophages. These results suggest that SARS-CoV-2 spike protein S1 subunit activates TLR4 signaling induce pro-inflammatory responses in murine and human macrophages. Therefore, TLR4 signaling in mac phages may be a potential target for regulating excessive inflammation in COVID-19 patients.

1. Introduction

Coronavirus disease 2019 (COVID-19), which has now spread globally, is an infectious disease caused by a novel type of coronavirus referred as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-

increased proportion of recruited pro-inflammatory monocyte-deriv macrophages in the bronchoalveolar lavage fluid [5]. Therefore, it estimated that a decline in clearance of dead lung cells and subseque diffusion of pro-inflammatory lipid mediators from these cells media the dysregulated recruitment and pro-inflammatory activation

Inflammation

Acute versus chronic

An increase in inflammation activation and signaling is associated with an increase in cancer **development**, **progression**, and **metastasis**; but, the stage of infection and the level of inflammation present is what is distinct between them.

- Nuclear factor kappa B (NF-κB)
- Interleukin-6 (IL-6)
- Toll-Like Receptor 4 (TLR4)
- NETosis

vaccines

MDPI

Communication

Nucleocapsid and Spike Proteins of the Coronavirus SARS-CoV-2 Induce *IL6* in Monocytes and Macrophages—Potential Implications for Cytokine Storm Syndrome

Iwona Karwaciak [1,†], Anna Sałkowska [2,†], Kaja Karaś [2], Jarosław Dastych [3] and Marcin Ratajewski [2,*]

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* Correspondence: mratajewski@cbm.pan.pl; Tel.: +48-42-209-3389
† These authors contributed equally to this work.

Abstract: The pandemic of the new coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has led to the deaths of more than 1.5 million people worldwide. SARS-CoV-2 causes COVID-19, which exhibits wide variation in the course of disease in different people, ranging from asymptomatic and mild courses to very severe courses that can result in respiratory failure and

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www.nature.com/cr
www.cell-research.com

Cell Research

LETTER TO THE EDITOR

SARS-CoV-2 spike protein interacts with and activates TLR41

Cell Research (2021) 31:818–820; https://doi.org/10.1038/s41422-021-00495-9

Dear Editor,

Accumulating clinical data suggest the main causes of death by COVID-19 include respiratory failure and the onset of sepsis.[1] Importantly, sepsis has been observed in nearly all deceased patients.[2–5] It remains elusive how SARS-CoV-2 infection results in viral sepsis in humans. Toll-like receptor 4 (TLR4) mediates anti-gram-negative bacterial immune responses by recognizing lipopolysaccharide (LPS) from bacteria.[6] We recently found that SARS-CoV-2 infection provoked an anti-bacterial like response at the very early stage of infection via TLR4. However, the identity of the original trigger initiating these abnormal immune responses during SARS-CoV-2 infection is unknown.

Previous in silico studies predicted cell surface TLRs, especially TLR4, are most likely to be involved in recognizing molecular patterns, probably spike protein, from SARS-CoV-2 to induce inflammatory responses.[7,8] Consistently, we found that the induction of IL1B by SARS-CoV-2 was completely blocked by TLR4-specific inhibitor Resatorvid (Fig. 1a). Combined with our recent data that TLR4 signaling was activated by SARS-CoV-2, we hypothesized that spike protein could activate TLR4 pathway. A recent study has reported that trimeric SARS-CoV-2 spike proteins are high quality antigens.[9] To this end, we purified the trimeric spike protein (1–1208 aa) (Fig. 1b; Supplementary information, Fig. S1a), as this form of spike protein presents on the surface of viral particle, which most able to suppress IL1B induced by spike protein (Supplementary information, Fig. S1f), suggesting that NF-κB was involved in this immune response. Trypsin digestion almost completely abolished the activation of IL1B by spike protein ruling out the possibility that the protein was contaminated by LPS (Fig. 1j; Supplementary information, Fig. S1g). Collectively, SARS-CoV-2 spike protein is capable of interacting with and activating TLR4.

To determine if other coronaviruses could activate TLR4 signaling, we treated THP-1 cells with murine coronavirus MHV-A59. As expected, MHV-A59 significantly induced IL1B (Fig. 1k), which was blocked by Resatorvid (Supplementary information, Fig. S1h). Theoretically, there is no MHV-A59 receptor (murine *Ceacam1*) expression in THP-1 cells, so MHV-A59 was not able to infect and enter this type of human monocytes. To confirm this, we washed those cells following the treatment with virus. After washing with PBS, the viral load was significantly decreased, so was the induction of IL1B (Fig. 1l; Supplementary information, Fig. S1i). These data suggested that MHV-A59 could trigger TLR4 signaling probably via spike–TLR4 interaction. Moreover, we treated macrophages with the spike protein trimer of SARS-CoV or infected these cells with human coronavirus 229E (HCoV-229E; Fig. 1m, n). Both treatments can induce production of IL1B, which was suppressed by Resatorvid. Together, different coronaviruses were able to activate TLR4 via their spike proteins.

Inflammation

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An increase in inflammation activation and signaling is associated with an increase in cancer **development**, **progression**, and **metastasis**; but, the stage of infection and the level of inflammation present is what is distinct between them.

Immunomodulation

(T cell and NK cell exhaustion)

Both acute and chronic inflammation are the result of the SARS-CoV-2 virus. The **paradox** here is that immune cell **exhaustion** can occur at the same time.

- Decrease in T cell number
- T cell exhaustion
- Decrease in NK cell number
- NK cell exhaustion
- Immune checkpoint up-regulation

Inflammopharmacology (2021) 29:343–366
https://doi.org/10.1007/s10787-021-00796-w

Inflammopharmacology

REVIEW

Cancer vs. SARS-CoV-2 induced inflammation, overlapping functions, and pharmacological targeting

Sreedhar Amere Subbarao[1]

Received: 28 September 2020 / Accepted: 27 February 2021 / Published online: 15 March 2021

Abstract
Inflammation is an intrinsic defence mechanism triggered by the immune system against infection or injury. Chronic inflammation allows the host to recover or adapt through cellular and humoral responses, whereas acute inflammation leads to cytokine storms resulting in tissue damage. In this review, we present the overlapping outcomes of cancer inflammation with virus-induced inflammation. The study emphasises how anti-inflammatory drugs that work against cancer inflammation may work against the inflammation caused by the viral infection. It is established that the cytokine storm induced in response to SARS-CoV-2 infection contributes to disease-associated mortality. While cancer remains the second among the diseases associated with mortality worldwide, cancer patients' mortality rates are often observed upon extended periods after illness, usually ranging from months to years. However, the mortality rates associated with COVID-19 disease are robust. The cytokine storm induced by SARS-CoV-2 infection appeared to be responsible for the multi-organ failure and increased mortality rates. Since both cancer and COVID-19 disease share overlapping inflammatory mechanisms, repurposing some anticancer and anti-inflammatory drugs for COVID-19 may lower mortality rates. Here, we review some of these inflammatory mechanisms and propose some potential chemotherapeutic agents to intervene in them. We also discuss the repercussions

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Mohammed *et al.*
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Cell Communication and Signaling

REVIEW Open Access

A comprehensive review about immune responses and exhaustion during coronavirus disease (COVID-19)

Rebar N. Mohammed[1,2], Rozita Tamjidifar[7], Heshu Sulaiman Rahman[4,5], Ali Adili[6], Shadi Ghoreishizadeh[7], Hossein Saeedi[7], Lakshmi Thangavelu[8], Navid Shomali[7], Ramin Aslaminabad[9], Faroogh Marofi[7], Mina Tahavvori[7], Svetlana Danshina[3], Morteza Akbari[7*] and Gülinnaz Ercan[9,10*]

Abstract

Coronavirus disease (COVID-19) is a viral infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The infection was reported in Wuhan, China, in late December 2019 and has become a major global concern due to severe respiratory infections and high transmission rates. Evidence suggests that the strong interaction between SARS-CoV-2 and patients' immune systems leads to various clinical symptoms of COVID-19. Although the adaptive immune responses are essential for eliminating SARS-CoV-2, the innate immune system may, in some cases, cause the infection to progress. The cytotoxic $CD8^+$ T cells in adaptive immune responses demonstrated functional exhaustion through upregulation of exhaustion markers. In this regard, humoral immune responses

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- NK cell exhaustion
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Molecular Therapy
Methods & Clinical Development
Original Article

Enhanced expression of immune checkpoint receptors during SARS-CoV-2 viral infection

Narjes Saheb Sharif-Askari,[1] Fatemeh Saheb Sharif-Askari,[1] Bushra Mdkhana,[1] Saba Al Heialy,[2,3] Habiba S. Alsafar,[4,5,6] Rifat Hamoudi,[1,7] Qutayba Hamid,[1,3,7] and Rabih Halwani[1,7,8]

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The immune system is tightly regulated by the activity of stimulatory and inhibitory immune receptors. This immune homeostasis is usually disturbed during chronic viral infection. Using publicly available transcriptomic datasets, we conducted *in silico* analyses to evaluate the expression pattern of 38 selected immune inhibitory receptors (IRs) associated with

different geographical regions, different sexes, age groups, and comorbidities, while its severity level ranged from asymptomatic infection to life-threatening disease.[4–7] Most patients were of an older age group (approximate age range of 30–79 years) and had mild symptoms, while 14% developed severe symptoms, and around 5% developed critical disease with a high mortality rate.[8] Severe COVID-19

Immunomodulation

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frontiers | Frontiers in Oncology

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Evidence of exhausted lymphocytes after the third anti-SARS-CoV-2 vaccine dose in cancer patients

Javier David Benitez Fuentes[1*†], Kauzar Mohamed Mohamed[2†], Alicia de Luna Aguilar[1], Carlos Jiménez García[2], Kissy Guevara-Hoyer[2,3], Miguel Fernandez-Arquero[2,3], M Antonia Rodríguez de la Peña[2], Laura Garciía Bravo[2], Alejandro Francisco Jiménez Ortega[4], Paloma Flores Navarro[1], Jorge Bartolome Arcilla[1], Bárbara Alonso Arenilla[2], Elvira Baos Muñoz[5], Alberto Delgado-Iribarren García-Campero[5], María Montealegre Sanz[1], Silvia Sanchez-Ramon[2,3‡] and Pedro Perez Segura[1‡]

- Increase vulnerability
- TME immunosuppression
- Increased carcinogenesis risk
- “Awaken” Dormant cancer cells
- Increased progression
- Increased metastasis

frontiers in Immunology

MINI REVIEW
published: 02 March 2022
doi: 10.3389/fimmu.2022.838011

Check for updates

NETosis and Neutrophil Extracellular Traps in COVID-19: Immunothrombosis and Beyond

*Yuanfeng Zhu†, Xiaoli Chen† and Xin Liu**

Clinical Medical Research Center, Southwest Hospital, Army Military Medical University, Chongqing, China

Infection with SARS-CoV-2, the causative agent of the Coronavirus disease 2019 (COVID-19) pandemic, causes respiratory problems and multifaceted organ dysfunction. A crucial mechanism of COVID-19 immunopathy is the recruitment and activation of neutrophils at the infection site, which also predicts disease severity and poor outcomes. The release of neutrophil extracellular traps (NETs), occurring during a regulated form of neutrophil cell death known as NETosis, is a key effector function that mediates harmful effects caused by neutrophils. Abundant NETosis and NET generation have been observed in the

NETosis

Neutrophil programmed cell death

“NETosis is a special form of **programmed cell death in neutrophils**, which is characterized by the extrusion of DNA, histones, and antimicrobial proteins in a web-like structure known as **neutrophil extracellular traps (NETs)**…increased generation of **reactive oxygen species (ROS)** is a crucial intracellular process that causes **NETosis**.”

- Increase vulnerability
- TME immunosuppression
- Increased carcinogenesis risk
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frontiers in Immunology

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NETosis

Neutrophil programmed cell death

“NETosis is a special form of **programmed cell death in neutrophils**, which is characterized by the extrusion of DNA, histones, and antimicrobial proteins in a web-like structure known as **neutrophil extracellular traps (NETs)**…increased generation of **reactive oxygen species (ROS)** is a crucial intracellular process that causes **NETosis**.”

Persistent

spike protein reservoirs

The culprit is not the persistent virus itself, but perhaps the **persistent presence** of the toxin that is the SARS-CoV-2 spike protein alone, whether sourced from **injection or Infection**.

- **Extracellular vesicles (EVs)**
- **Exosomes**
- **Lipid nanoparticles (LNP)**

Clinical Infectious Diseases

BRIEF REPORT

Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae

Zoe Swank,[1,2,3] Yasmeen Senussi,[1,2,3] Zachary Manickas-Hill,[4] Xu G. Yu,[1,4,5] Jonathan Z. Li,[1,5] Galit Alter,[4,6] and David R. Walt[1,2,3]

[1]Harvard Medical School, Boston, Massachusetts, USA; [2]Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts, USA; [3]Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, Massachusetts, USA; [4]Ragon Institute of MGH, MIT and Harvard, Cambridge, Massachusetts, USA; [5]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA; and [6]Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, USA

The diagnosis of postacute sequelae of coronavirus disease 2019 (PASC) poses an ongoing medical challenge. To identify biomarkers associated with PASC we analyzed plasma samples collected from PASC and coronavirus disease 2019 patients to quantify viral antigens and inflammatory markers. We detect severe acute respiratory syndrome coronavirus 2 spike predominantly in PASC patients up to 12 months after diagnosis.

Keywords. COVID-19; post-acute sequelae of COVID-19 (PASC); long COVID; SARS-CoV-2 antigens; spike.

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFOR

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Disentangling the complex biology of PASC will rely on t
identification of biomarkers that enable classification of patie
phenotypes. Here, we measure SARS-CoV-2 antigen and cyt
kine levels in plasma samples collected from individuals infect
with SARS-CoV-2, some of whom developed PASC.

METHODS

A retrospective pilot study was performed using plasma sa
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COVID-19 or PASC. A full description of the patient coh
and sample collection is provided in the Supplementa
Materials. SARS-CoV-2 antigens and a panel of 10 cytokir
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RESULTS

We analyzed plasma samples from a cohort of 63 individu
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Immunoediting

- Elimination
- Equilibrium
- Escape

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New insights into cancer immunoediting and its three component phases — elimination, equilibrium and escape

Deepak Mittal[1,4], **Matthew M Gubin**[2,4], **Robert D Schreiber**[2,5], and **Mark J Smyth**[1,3,5]

[1]QIMR Berghofer Medical Research Institute, Herston, 4006 Queensland, Australia

[2]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA

[3]School of Medicine, University of Queensland, Herston, 4006 Queensland, Australia

Abstract

The principles of cancer immunoediting have set the foundations for understanding the dual host-protective and tumor sculpting actions of immunity on cancer and establishing the basis for novel individualized cancer immunotherapies. During cancer immunoediting, the host immune system shapes tumor fate in three phases through the activation of innate and adaptive immune mechanisms. In the first phase, Elimination, transformed cells are destroyed by a competent immune system. Sporadic tumor cells that manage to survive immune destruction may then enter an Equilibrium phase where editing occurs. The Escape phase represents the third and final phase

Persistent

SARS-CoV-2 virus

"Persistent infections are characterized as those in which the virus is not cleared but remains in specific cells of infected individuals. Persistent infections may involve stages of both **silent** and **productive** infection without rapidly killing or even producing excessive damage of the host cells. There are three types of overlapping persistent virus-host interaction that may be defined as **latent, chronic and slow** infection."

Immunoediting

- Elimination
- Equilibrium
- Escape

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journal homepage: www.elsevier.com/locate/intimp

Immunoediting in SARS-CoV-2: Mutual relationship between the virus and the host

Nasim Kheshtchin [a,b], Parisa Bakhshi [c], Samaneh Arab [d,e], Maryam Nourizadeh [f,*]

[a] Department of Immunology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[c] Department of Medical Biotechnology, Faculty of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran
[d] Nervous System Stem Cells Research Center, Semnan University of Medical Sciences, Semnan, Iran
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COVID-19
Immune response
SARS-CoV-2
Viral infection

ABSTRACT

Immunoediting is a well-known concept that occurs in cancer through three steps of elimination, equilibrium, and escape (3Es), where the immune system first suppresses the growth of tumor cells and then promotes them towards the malignancy. This phenomenon has been conceptualized in some chronic viral infections such as HTLV-1 and HIV by obtaining the resistance to elimination and making a persistent form of infected cells especially in untreated patients. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a heterogeneous disease characterizing from mild/asymptomatic to severe/critical courses with some behavioral aspects in an immunoediting setting. In this context, a coordinated effort between innate and adaptive immune system leads to detection and destruction of early infection followed by equilibrium between virus-specific responses and infected cells, which eventually ends up with an uncontrolled inflammatory response in severe/critical patients. Although the SARS-CoV-2 applies several escape strategies such as mutations in viral epitopes, modulating the interferon response and inhibiting the MHC I molecules similar to the cancer cells, the 3Es hallmark may not occur in all clinical conditions. Here, we discuss how the lesson learnt from cancer immunoediting and accurate understanding of these pathophysiological

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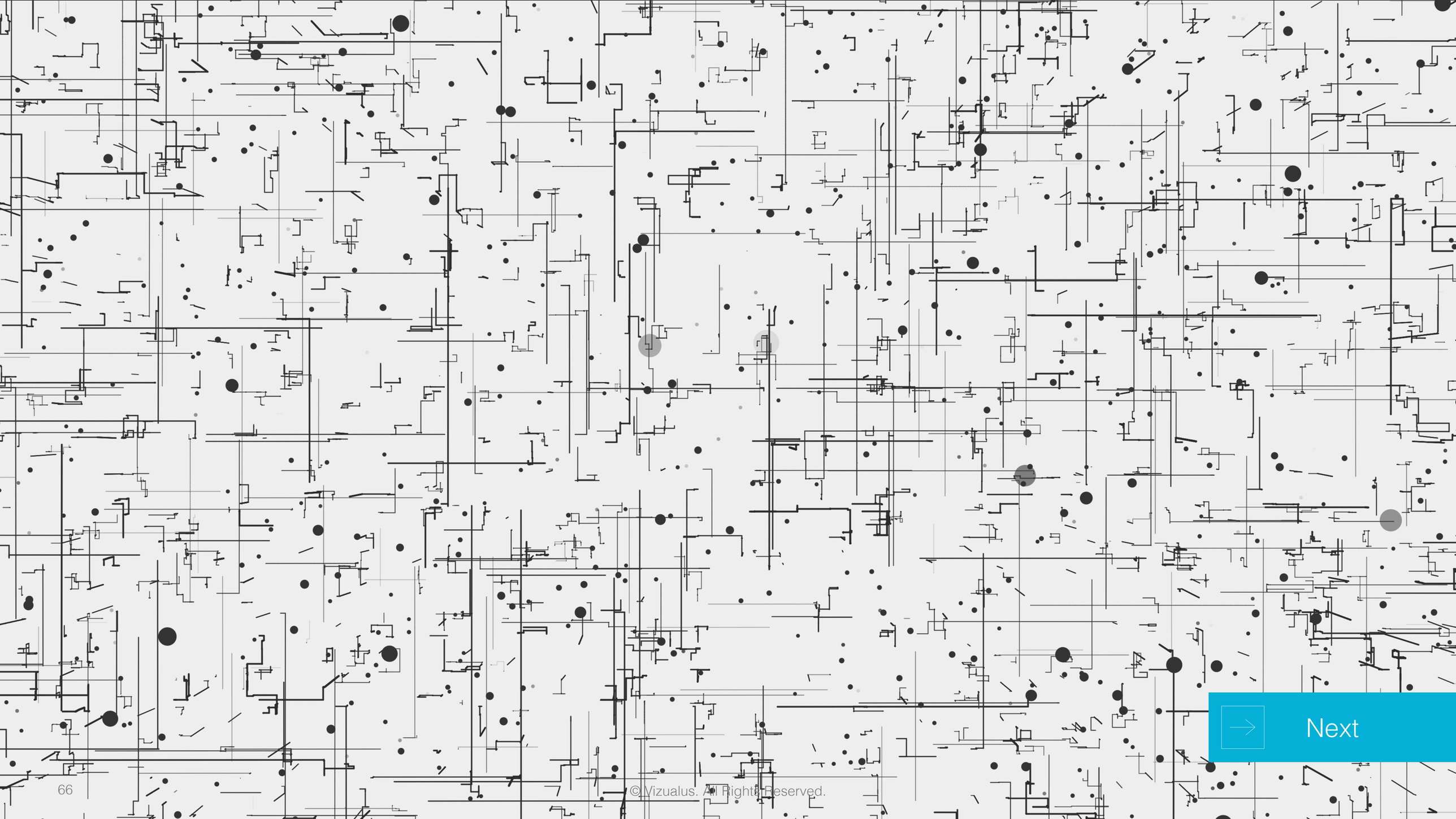

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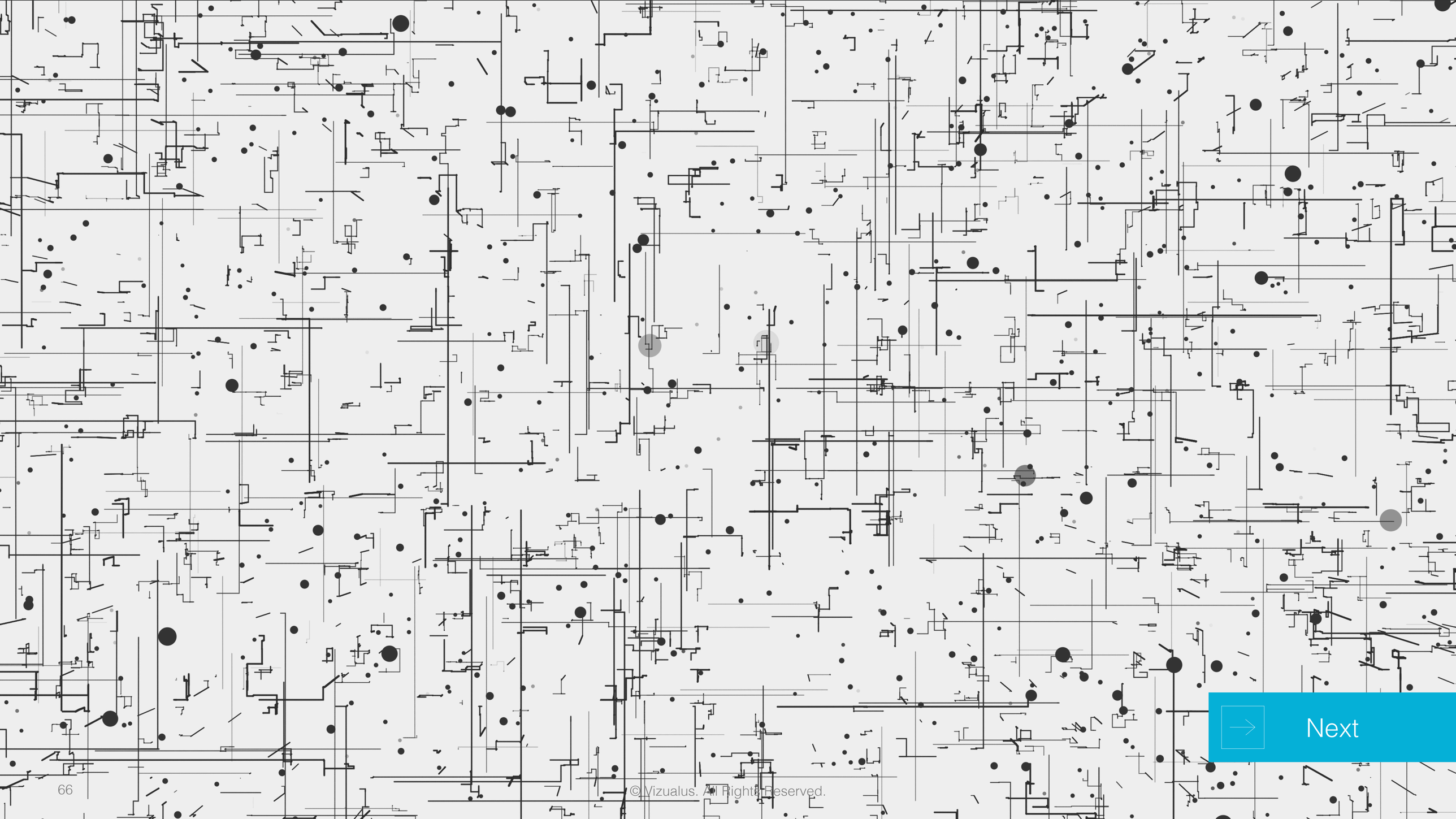

Next

SARS-CoV-2

Next

SARS-CoV-2 · Latent viral activation ·

Next

SARS-CoV-2 ·

· Latent viral activation ·

· OncoVirus activation

Next

SARS-CoV-2 ·

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· OncoVirus activation

Next

- transmission between humans
- chronic infection
- co-opts cellular processes
- undermines immune recognition
- derails signaling pathways
- supports propagation

6

What is an OncoVirus?

“causing the development of a tumor or tumors.”

“Human oncogenic viruses have diverse genomes, cellular tropisms, cancer pathologies and disease prevalence... However, they share many features that can lead to cancer in humans. They are 1) transmitted between humans and can 2) establish chronic infections that last for years without obvious symptoms. Throughout these prolonged periods, oncogenic viruses 3) co-opt cellular processes for replication and 4) undermine immune recognition. They 5) derail conserved signaling pathways that control cell cycle progression and apoptosis… to 6) support their propagation.” (From *Krump, NA, You J. Molecular mechanisms of viral oncogenesis in humans.*)

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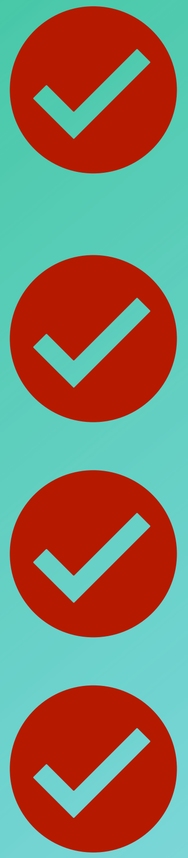

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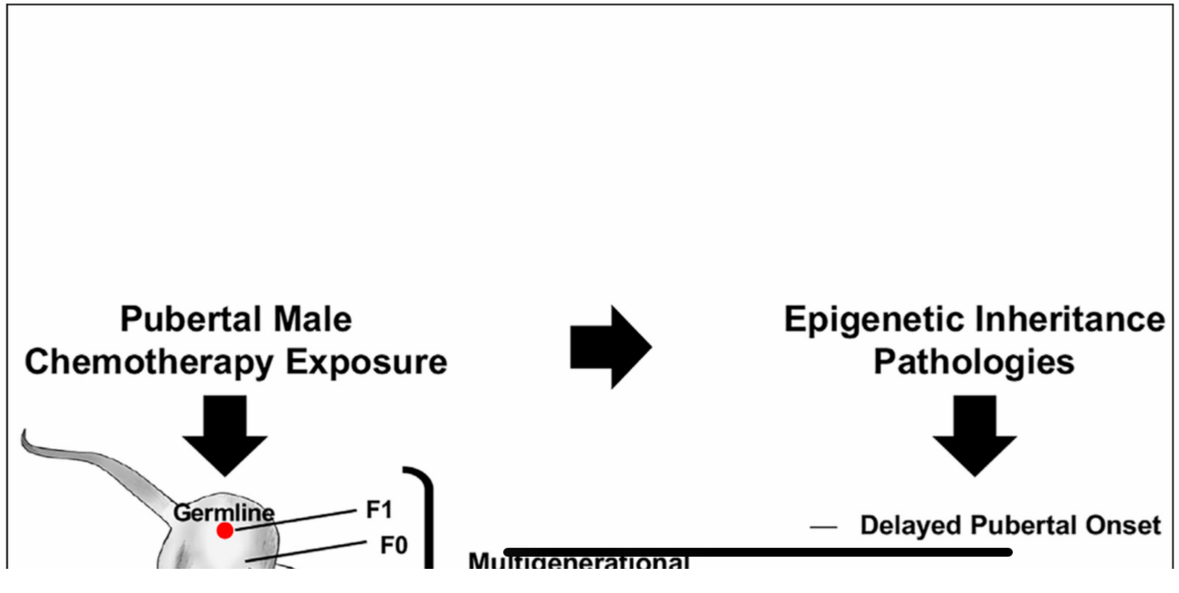
“Wherever the art of Medicine is loved, there is also a love of humanity.”

—Hippocrates

What is our legacy?

Article

Examination of generational impacts of adolescent chemotherapy: Ifosfamide and potential for epigenetic transgenerational inheritance



Ryan P. Thompson, Daniel Beck, Eric Nilsson, Millissia Ben Maamar, Margarett Shnorhavorian, Michael K. Skinner

skinner@wsu.edu

Highlights

Chemotherapy-induced sperm DNA methylation facilitates epigenetic

Epigenetic Transgenerational Inheritance of Pathology

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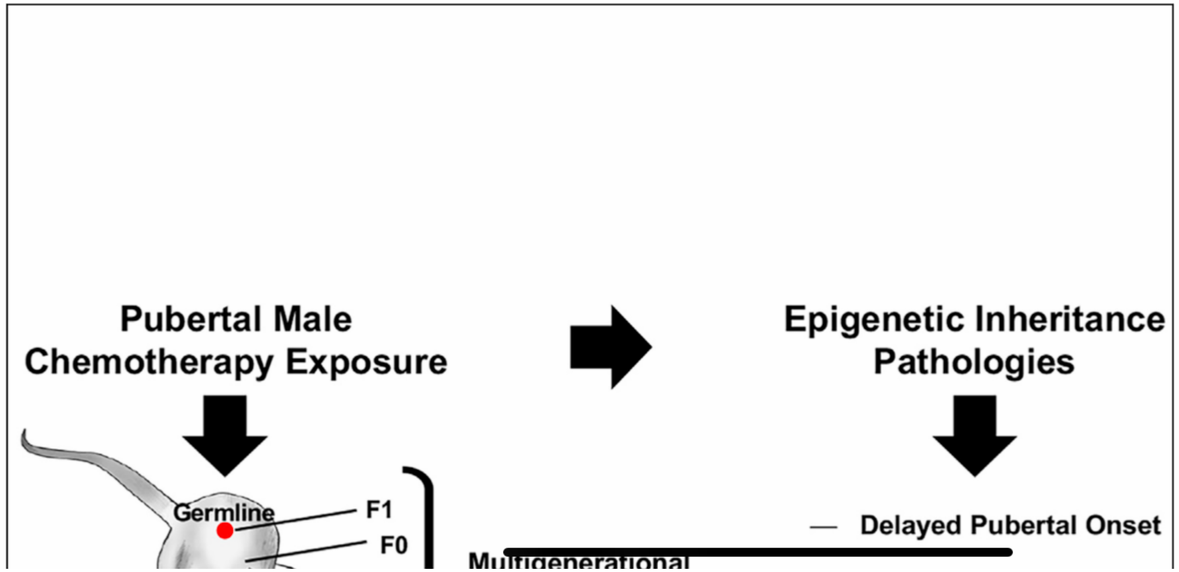

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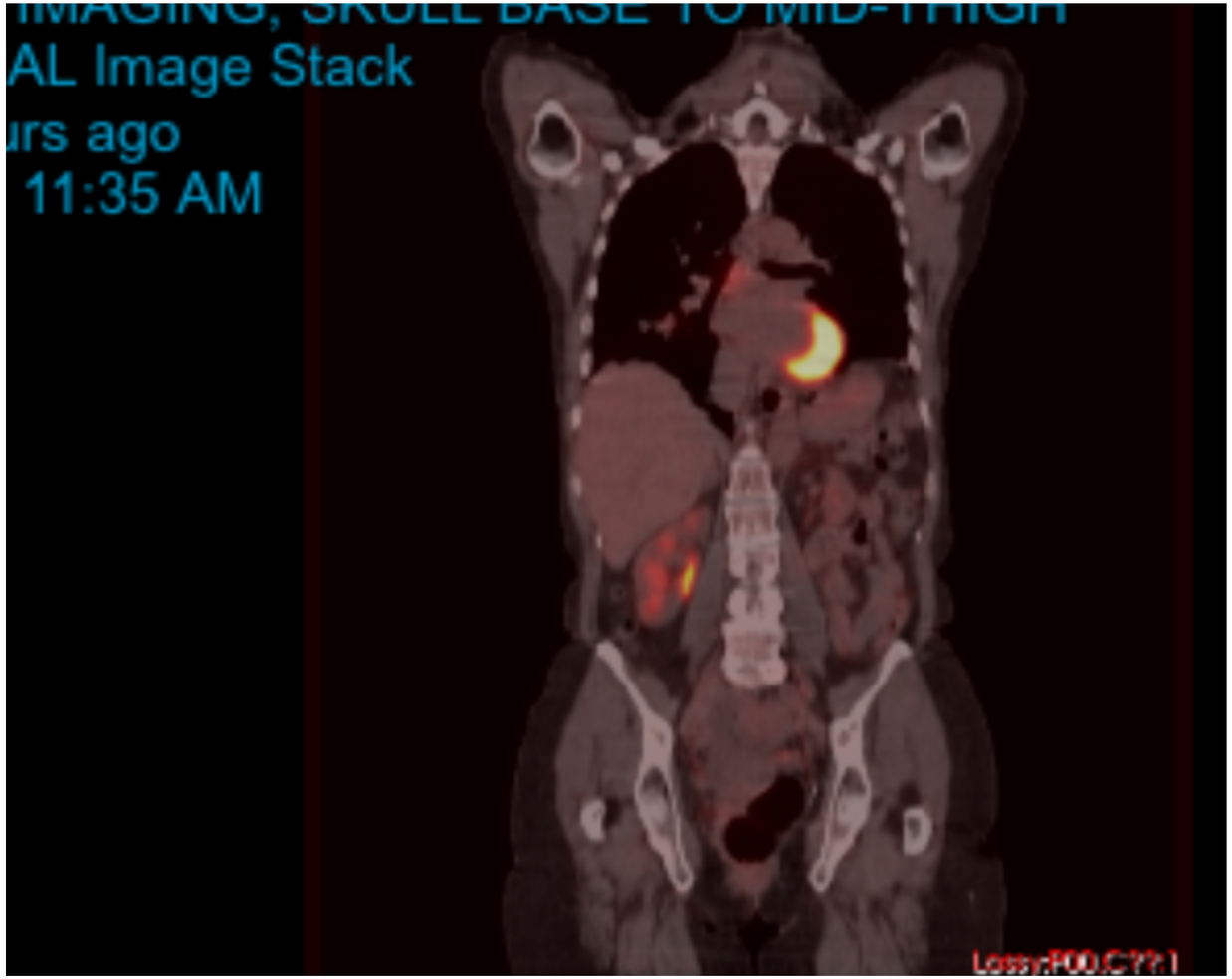
Case study #2

- Stage IV ER+/PR+/HER-2- recurrent breast cancer in 2020
- Widespread Liver, Lung, and Bone metastasis
- COVID infection November 2022
- Then…



PET/CT

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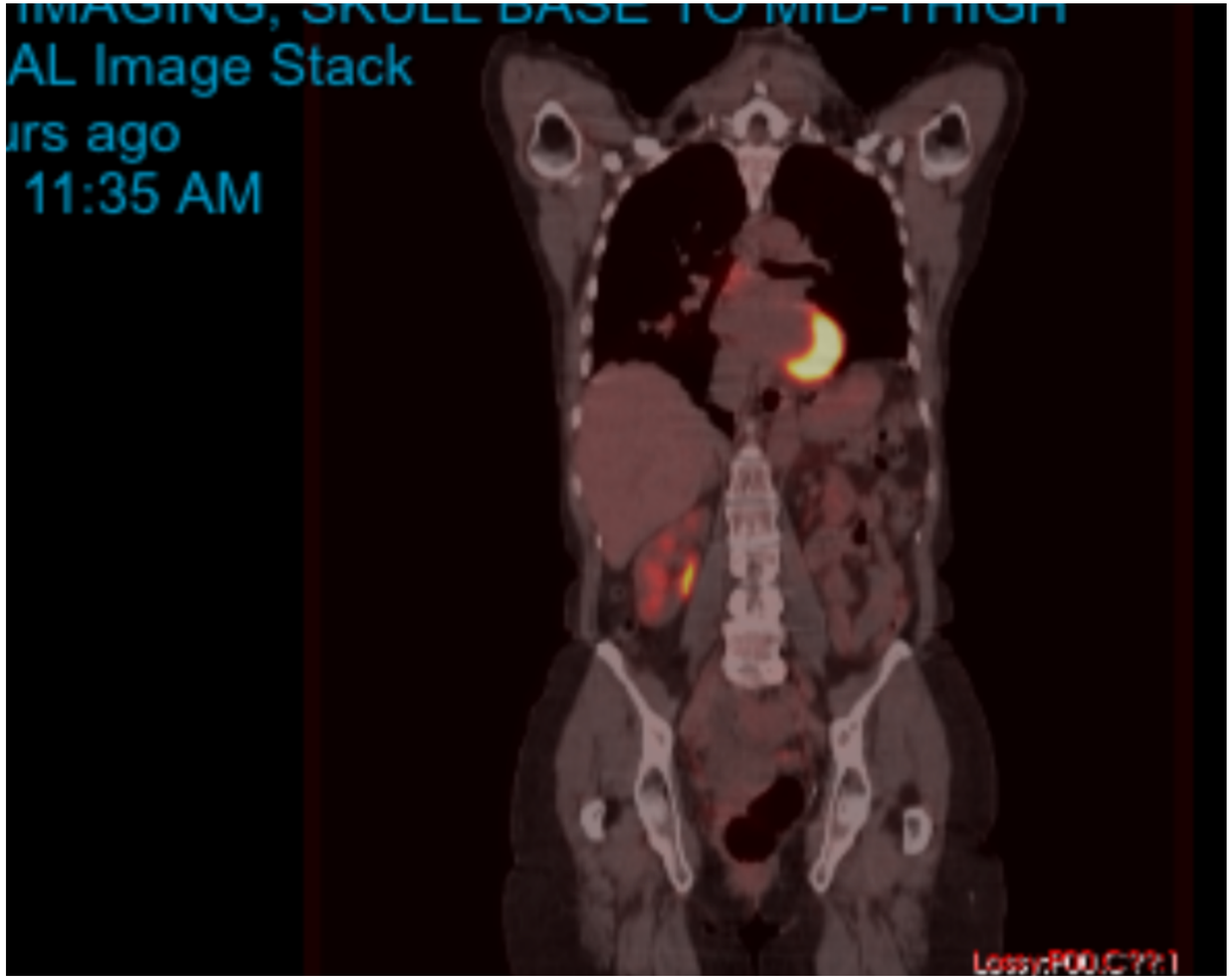

PET/CT

“Move in silence, speak only
when it is time to say

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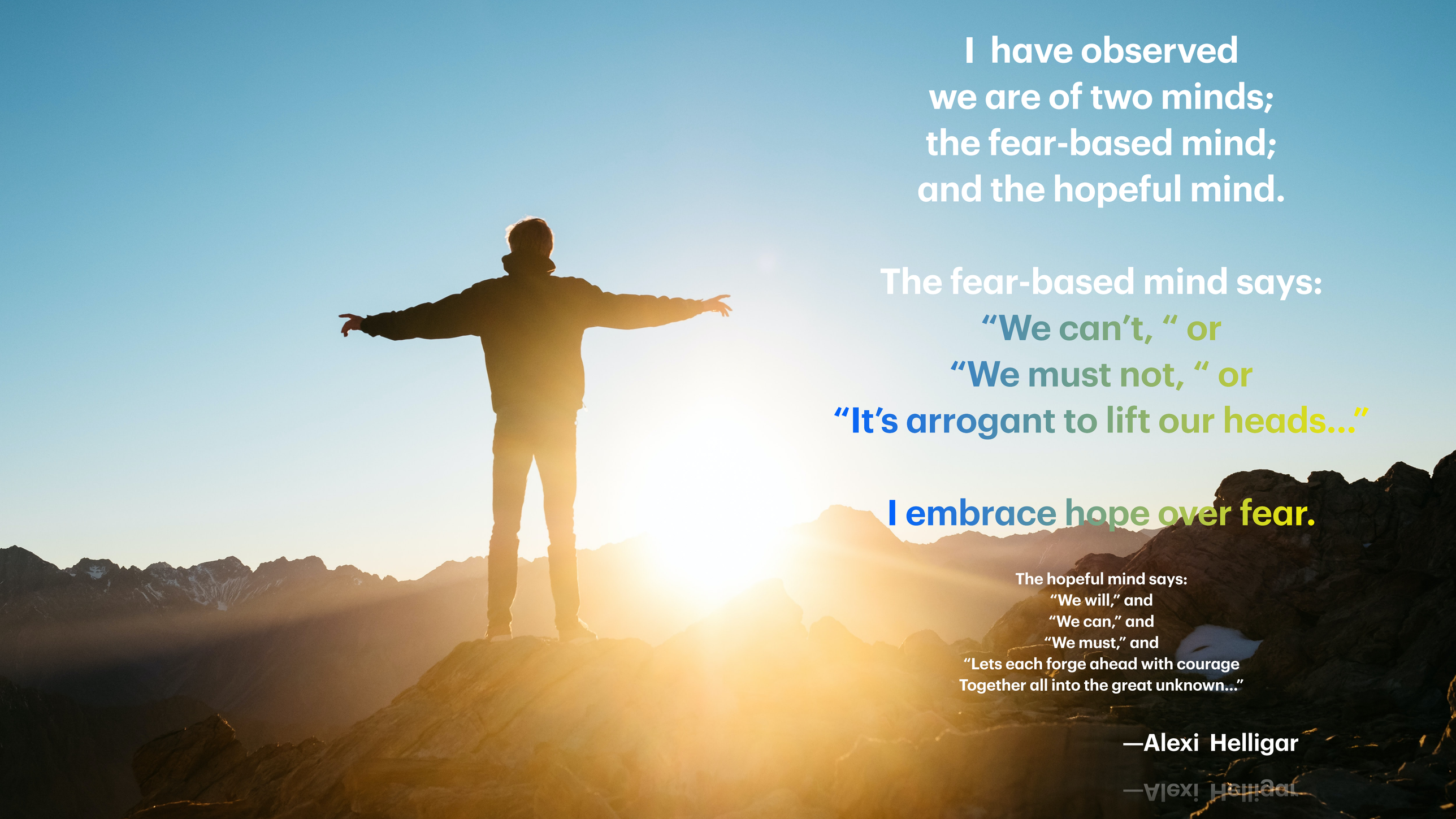
CheckMate!”



I have observed
we are of two minds;
the fear-based mind;
and the hopeful mind.

The fear-based mind says:
"We can't, " or
"We must not, " or
"It's arrogant to lift our heads..."

I embrace hope over fear.

The hopeful mind says:
"We will," and
"We can," and
"We must," and
"Lets each forge ahead with courage
Together all into the great unknown..."

—Alexi Helligar

Prevention

mid-15c., *prevencioun*, "action of stopping an event or practice," from Medieval Latin *preventionem* (nominative *preventio*) "action of anticipating; **a going before**," noun of action from past-participle stem of Latin *praevenire* "come or go before, **anticipate**" . Original sense in English now is obsolete; the meaning "act of hindering or rendering

01

LIFESTYLE

- Nutrition
- Sleep
- Exercise

02

SUPPLEMENTS

- Vitamin D
- Quercetin
- Vitamin C
- Beta-glucagon
- Artemisinin
- Nattokinase
- Zinc
- CBD

03

MEDICATIONS

- Ivermectin
- Mebendazole
- Hydroxychloroquine
- Azithromycin
- Doxycycline
- Liothyronine (T3)
- Metformin

04

PEPTIDES

- Off the shelf (TA-1)
- Custom, precision peptides

Monitoring

1540s, "senior pupil at a school charged with keeping order, etc.," from Latin *monitor* "one who reminds, admonishes, or checks," also "an **overseer**, **instructor**, **guide**, **teacher**," agent noun from *monere* "to remind, bring to (one's) recollection, tell (of); admonish, advise, warn, instruct, teach," from PIE **moneie-* "to make think of, remind" (source

01

EDUCATION

Healing begins with teaching. One must be informed how to heal oneself. In turn, one must be informed to know when one needs healing.

02

CONVENTIONAL LABS

- CBC, CMP
- MPO
- Ferritin
- D-Dimer
- HSCRP
- Lymphocytes
- Cytokines
- Vitamin D3
- Vitamin A
- ANA

03

SPECIALTY LABS

Specialty labs allow a deeper look under the metabolic and immune hood of cancer. Cancer biomarkers have poor reliability at best.

- Signatera molecular residual disease (MRD) with circulating tumor cT DNA
- Galleri test

04

COVID ANTIGEN TESTING

We do after all have to confirm the presence of the SARS-CoV-2 virus. It is an Oncovirus. We must confirm its presence to start immediate and early intervention.

Early Intervention

early 15c., *intervencioun*, "intercession, intercessory prayer," Late Latin *interventionem* (nominative *interventio*) "an interposing, a giving security," literally "a coming between," noun of action from past-participle stem of Latin *intervenire* "**to come between, interrupt**," from *inter* "between", "to come", “act of intervening”…

01

PEPTIDES

A peptide is defined as a short chain of amino acids (typically 2 to 50). Polypeptides are defined as a “large” number of peptides joined in a polymer existing in “off the shelf” and “precision” design.

02

PHOTODYNAMIC THERAPY

A light-based technology first officially acknowledged in 1903, though used for over a millennium, that uses 3 main elements: a 1) photosensitizer, 2) light, and 3) oxygen. The end result is the triggering of photochemical reactions.

03

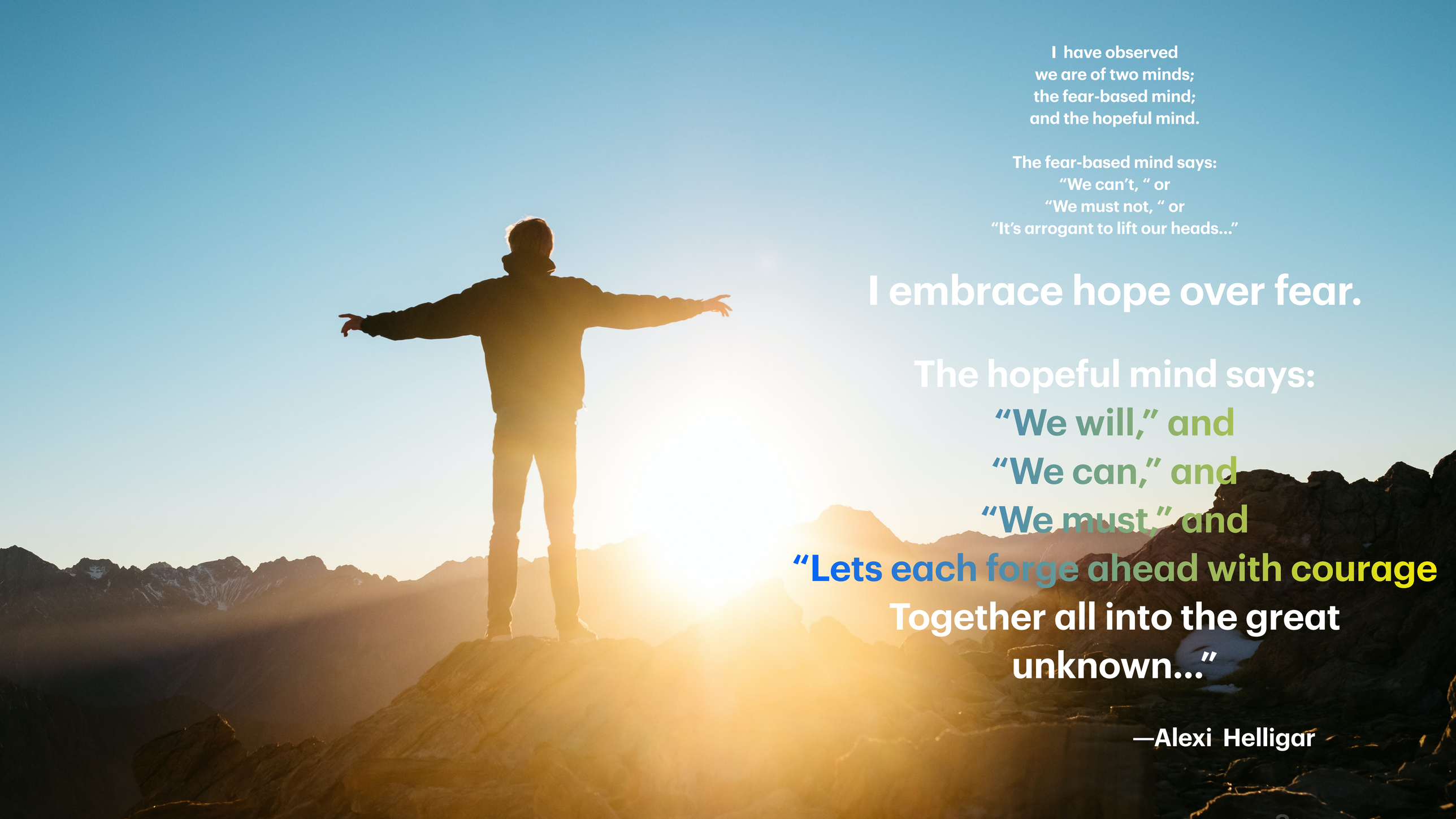
TARGETED SUPPLEMENTATION

Vitamin C: broad anti-infectious activity, anti-parasitic, anti-bacterial, and anti-viral activity..
Indole-3-carbonyl (I3C): “..one of the potent antiviral agents that can reduce S-mediated metastasis.”
NF-κB pathway inhibitors: Pharmacologic inhibition of NF-κB activity suppressed viral replication and Gamma variant-mediated breast cancer metastasis.

04

OZONE

“Ozone exerts antiviral activity through the inhibition of viral replication and direct inactivation of viruses. Ozone is an antiviral drug enhancer…Combined treatment with involving ozone and antivirals demonstrated a reduction in inflammation and lung damage.”



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“If early detection of cancer is important; early detection of COVID is equally important.”

—Garland Carter

Thank

You!