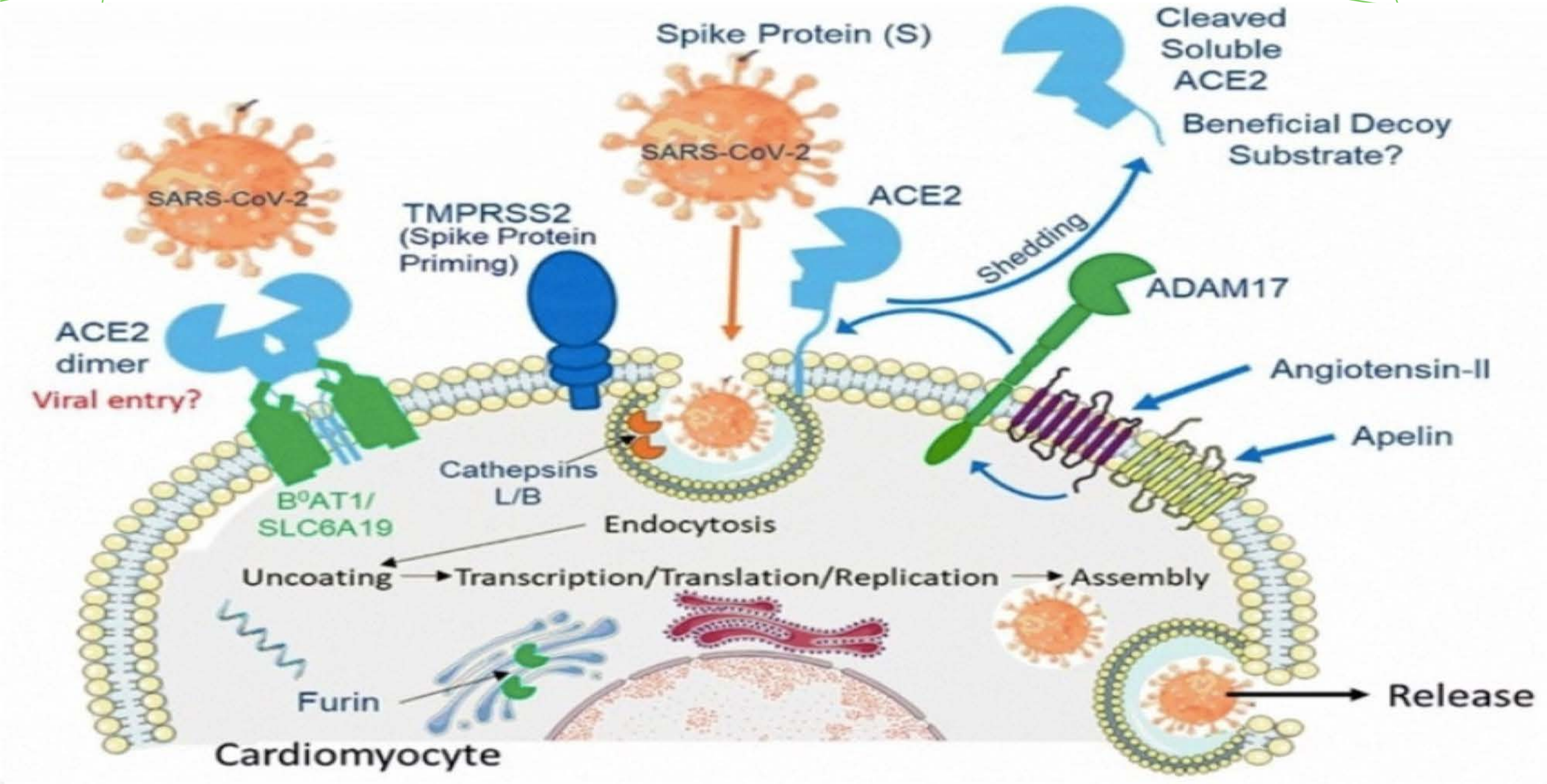
REAL CHANGES YOU CAN MAKE NOW TO *CONTROL YOUR COVID OUTCOME*

PERSONALIZED COVID TREATMENT PLANS DEVELOPED FROM LATEST SCIENCE

FUNCTIONAL
MEDICINE SPECIALISTS

Cambria DeMarco, ACNP-BC, MSN, BA, BSN
IFM Practitioner
Walsh & Bredesen Protocol Certified
www.fmscal.com

KEY PLAYER : THE SARS-COV2 VIRUS



The Underlying Cause: SARS-CoV-2

- An RNA virus that attacks cells by binding its surface protein (S-protein) to a receptor (ACE2 receptor/enzyme) on many human cells.

- The lungs are the most vulnerable organ because of the high percentage of cells expressing ACE2. 83% of the ACE2 expressing cells in the lungs produce surfactant, leading to hypoxia.

- ACE2 receptors are also found in the heart, kidney, olfactory endothelium, vascular endothelium, and intestine – explaining the correlation between infection and the seemingly disparate organ systems affected in COVID-19

Zhang, H., Penninger, J.M., Li, Y. et al. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 46, 586–590 (2020)

COVID-19

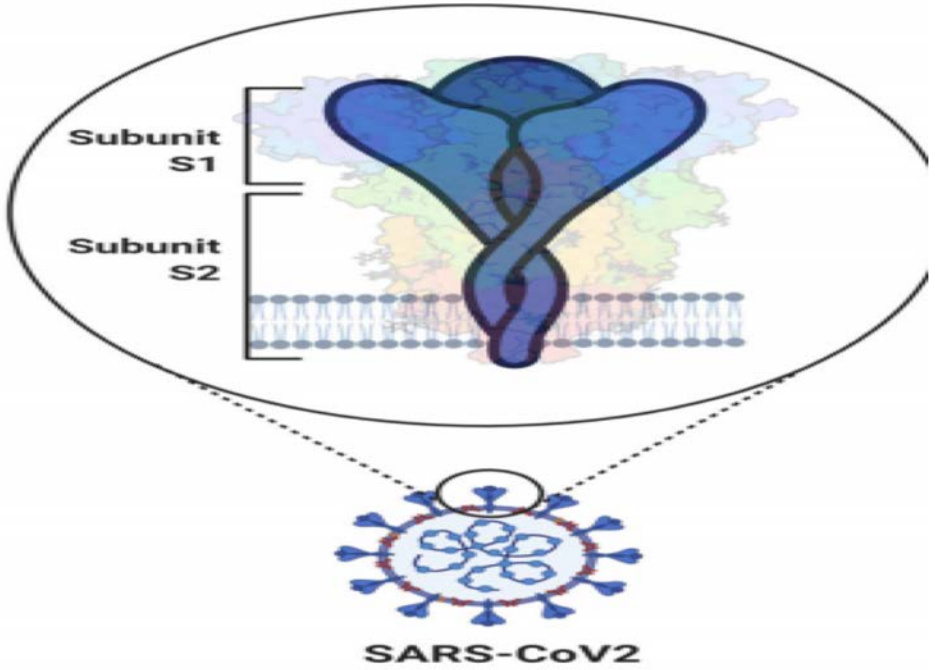
PATHOPHYSIOLOGY AND MECHANISMS

UNDERSTANDING THE VIRUS

EQUALS UNDERSTANDING WHERE WE CAN INTERVENE

- SPIKE PROTEIN CLEAVAGE
- *ACE-2 RECEPTOR DOCKING*
- *VIRAL ENTRY INTO THE CELL*
- *FUSION VS ENDOCYTOSIS*
- *TRANSCRIPTION AND TRANSLATION OF VIRAL RNA*
- *ASSEMBLY AND RELEASE OF VIRIONS*

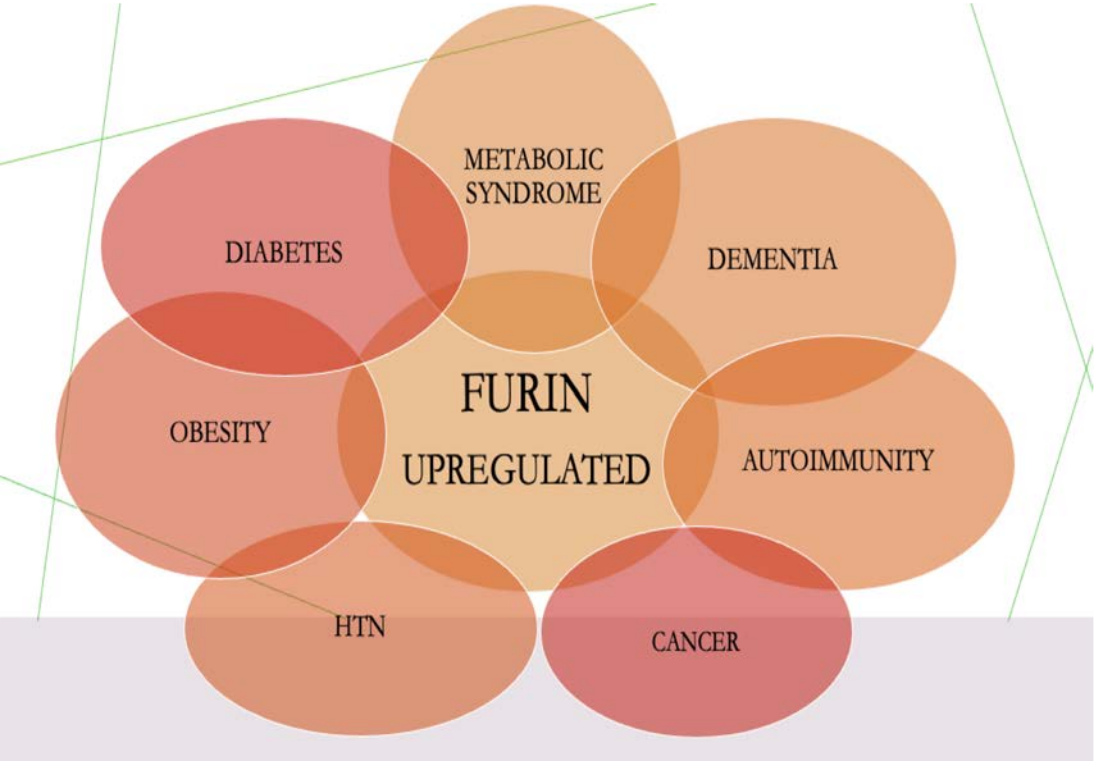
(EACH PHASE CAN BE A POTENTIAL TARGET FOR THERAPEUTICS)



A unique furin-like cleavage site (FCS) in the spike protein (S), is responsible for its high infectivity and transmissibility.

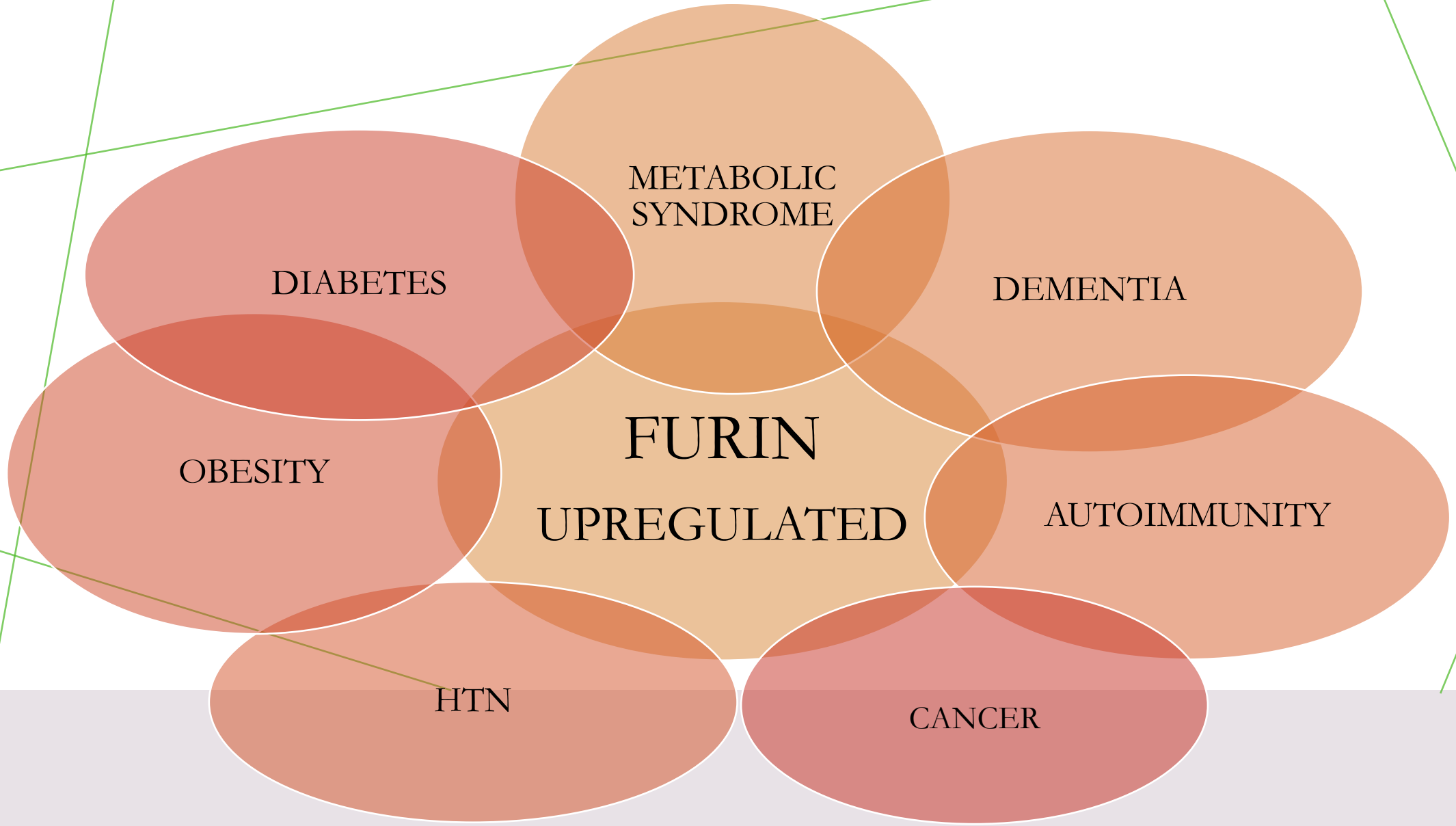
FURIN CLEAVES THE SPIKE PROTEIN

MECHANISM = PLACE TO INTERVENE

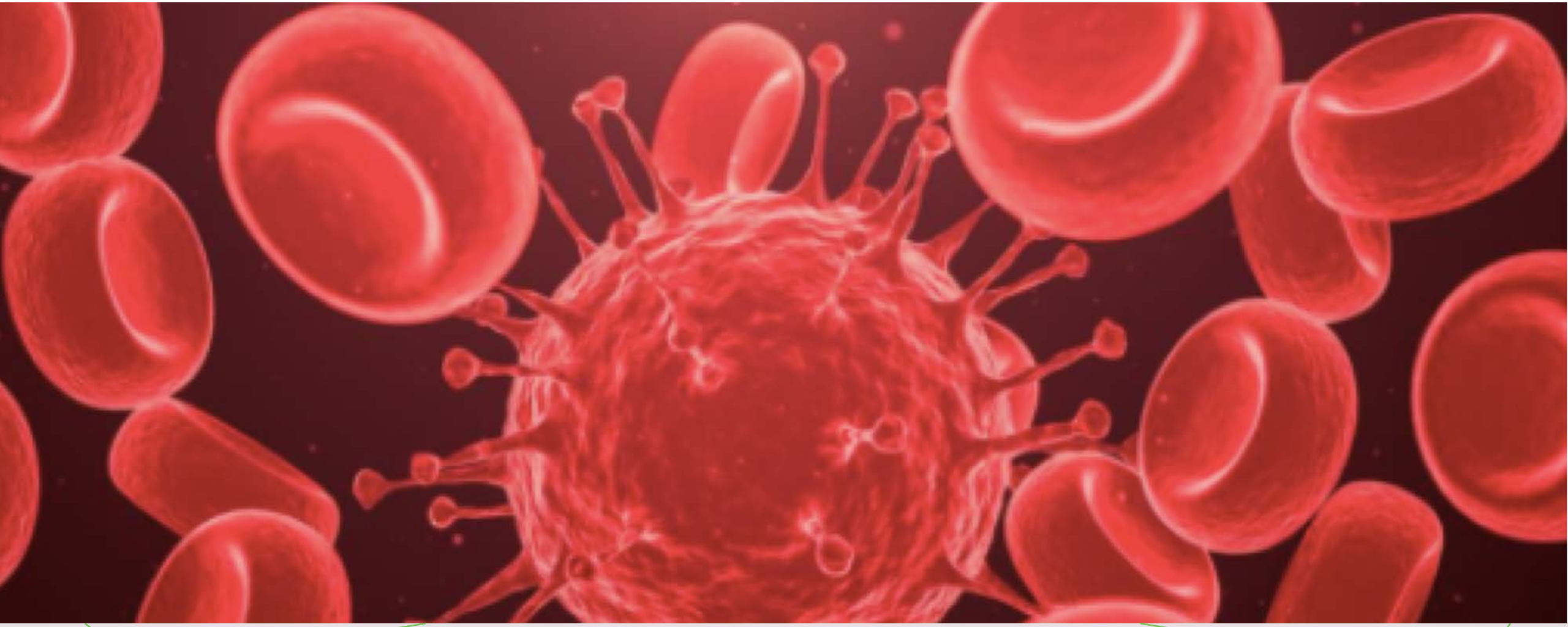


FURIN CLEAVES THE SPIKE PROTEIN OF SARS-COV-2 ALLOWING IT TO ENTER THE CELL

SECONDARY CLEAVAGE SITE : TRANSMEMBRANE PROTEASE, SERINE 2 (AKA: TMPRSS2)



ELEVATED FURIN MEANS MORE & FASTER CLEAVAGE OF SPIKE PROTEINS
WHICH MEANS IT IS EASIER FOR VIRUS TO DOCK AND ENTER THE CELL
ELEVATED FURIN MAKES ONE MORE SUSCEPTIBLE TO SEVERE SARS-COV-2 INFECTION



PATHOLOGY

ELEVATED FURIN ASSOCIATED WITH A PRO-COAGULATION STATE VIA ELEVATED VWF AND VIII : HENCE CLOTTING ISSUES

ELEVATED FURIN IS ALSO ASSOCIATED WITH ELEVATED PLASMIN

THE PATH AND THE BIOCHEMICAL CONSEQUENCES OF THE VIRUS

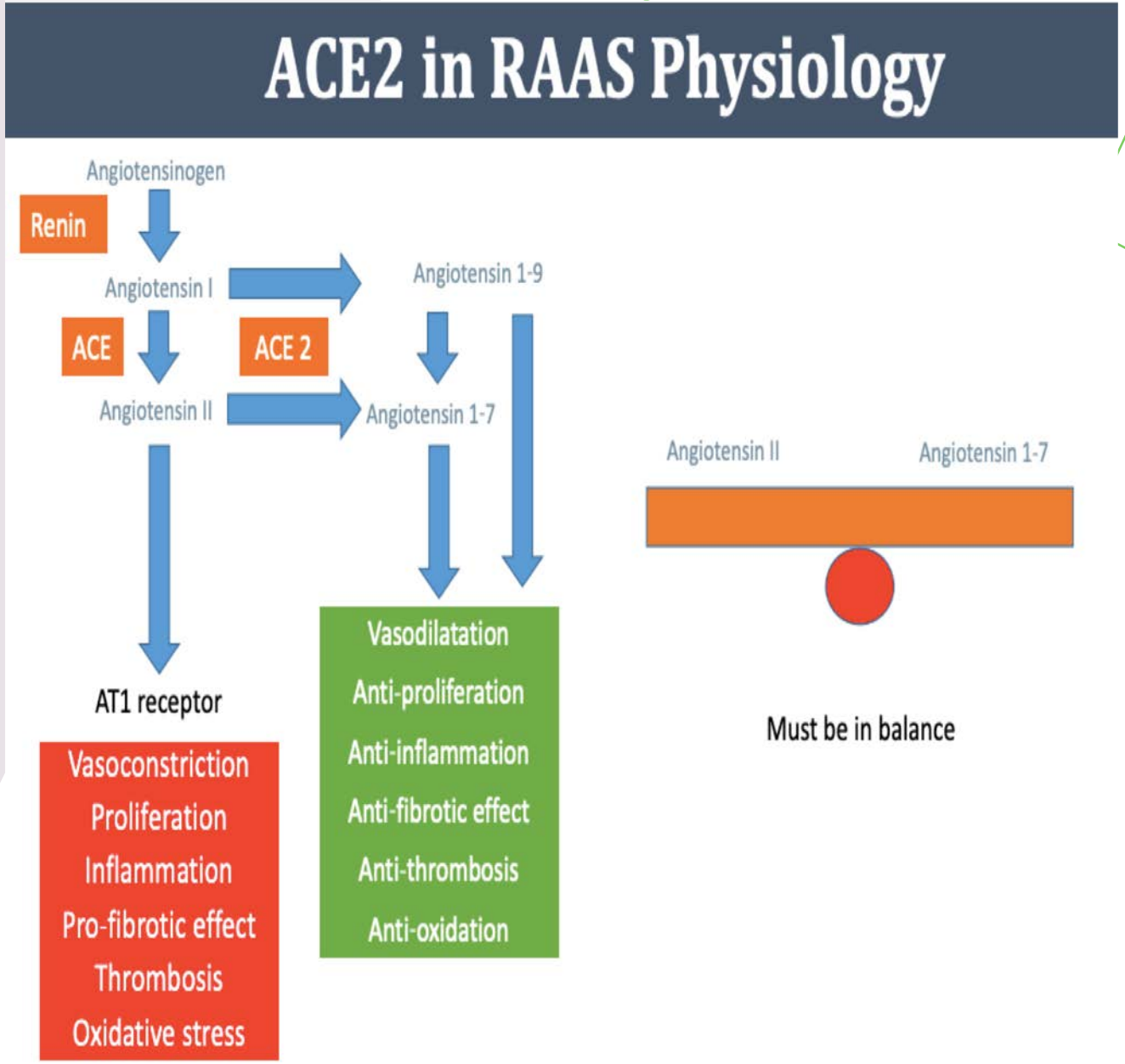
ACE-2 RECEPTOR = DOCKING SITE

AND BEGINNING OF THE PATHOLOGY

AFTER CLEAVED BY FURIN,
SARS-COV2 BINDS TO, AND DAMAGES ACE2 RECEPTOR/ENZYME COMPLEX,
ACE2 RECEPTOR/ENZYME GETS DOWN REGULATED (OR DECREASED)
RESULTING IN INCREASED ACTIVATION OF AT1 RECEPTOR

(PUSHES ANGIOTENSIN 2 PATHWAY DOMINANCE)

WE NEED BALANCE
FOR OPTIMAL FUNCTION



LOW ACE-2 IS ASSOCIATED WITH:

• DIABETES • CHF • CARDIOVASCULAR DISEASE

• OBESITY • OLDER PATIENTS • HYPERTENSION

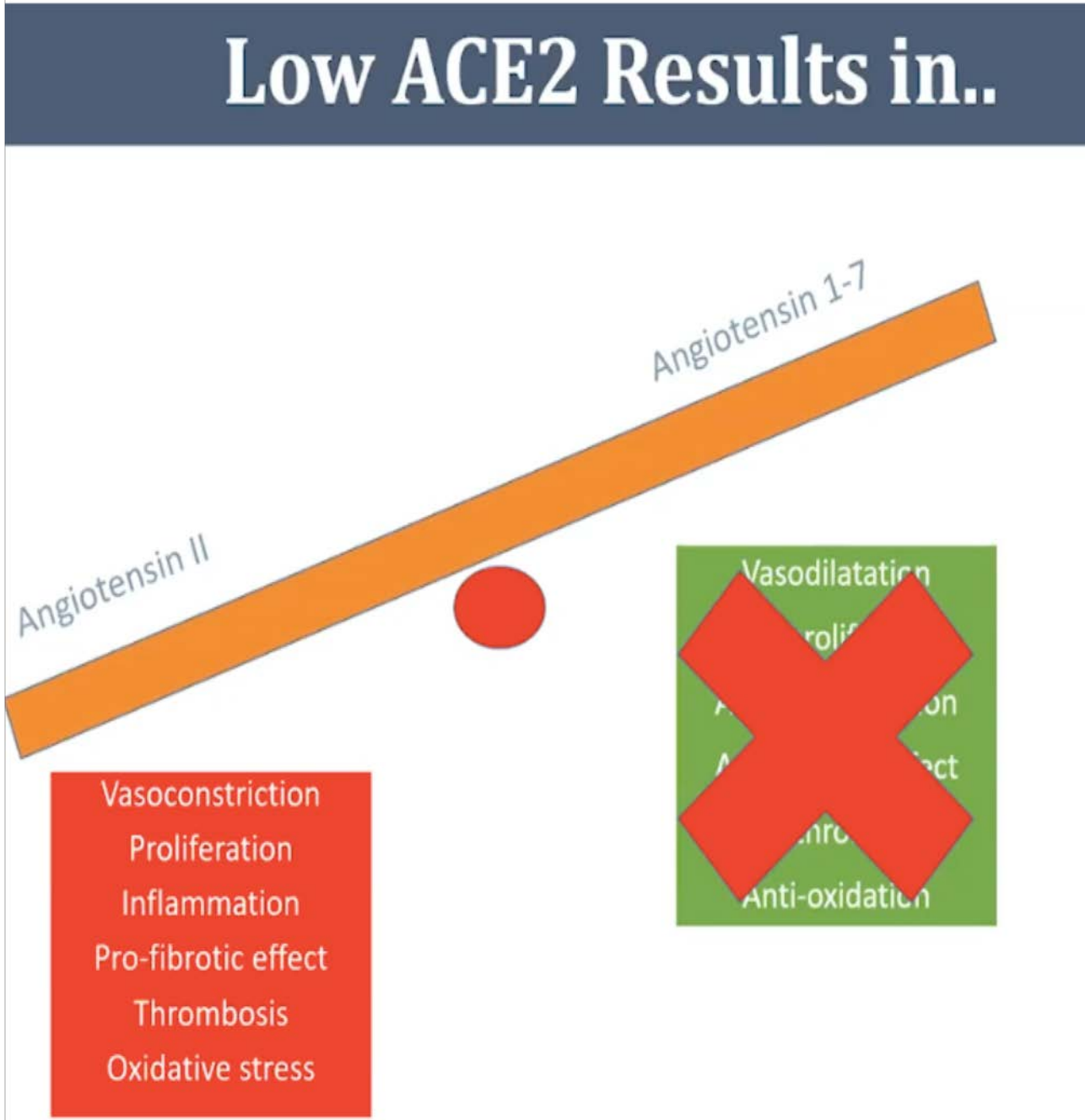
(HOW YOU DO, IS RELATED TO WHAT YOU COME TO THE TABLE WITH)

- *SARS-COV-2 INFECTION*

EFFECT ON ACE2 LEADS TO:

AN INCREASE IN ANGIOTENSIN II

(RESULTS IN VASOCONSTRICTION, PROLIFERATION, INFLAMMATION, OXIDATION, FIBROSIS AND THROMBOSIS)

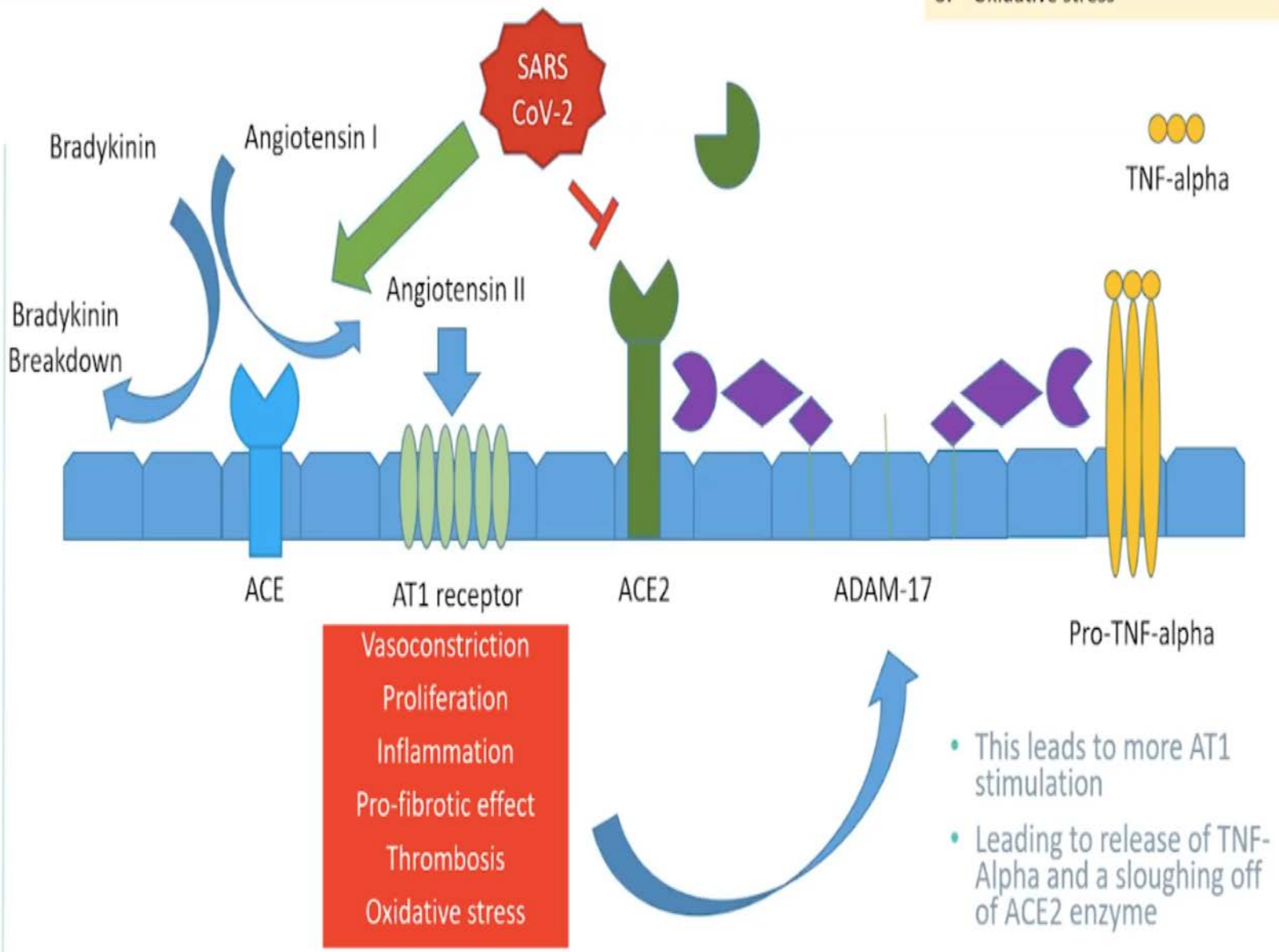


STARTS A NEGATIVE CASCADE

ADAM 17 is Activated

ADAM 17 activated by:

1. Angiotensin II
2. Hyperglycemia
3. Oxidative stress



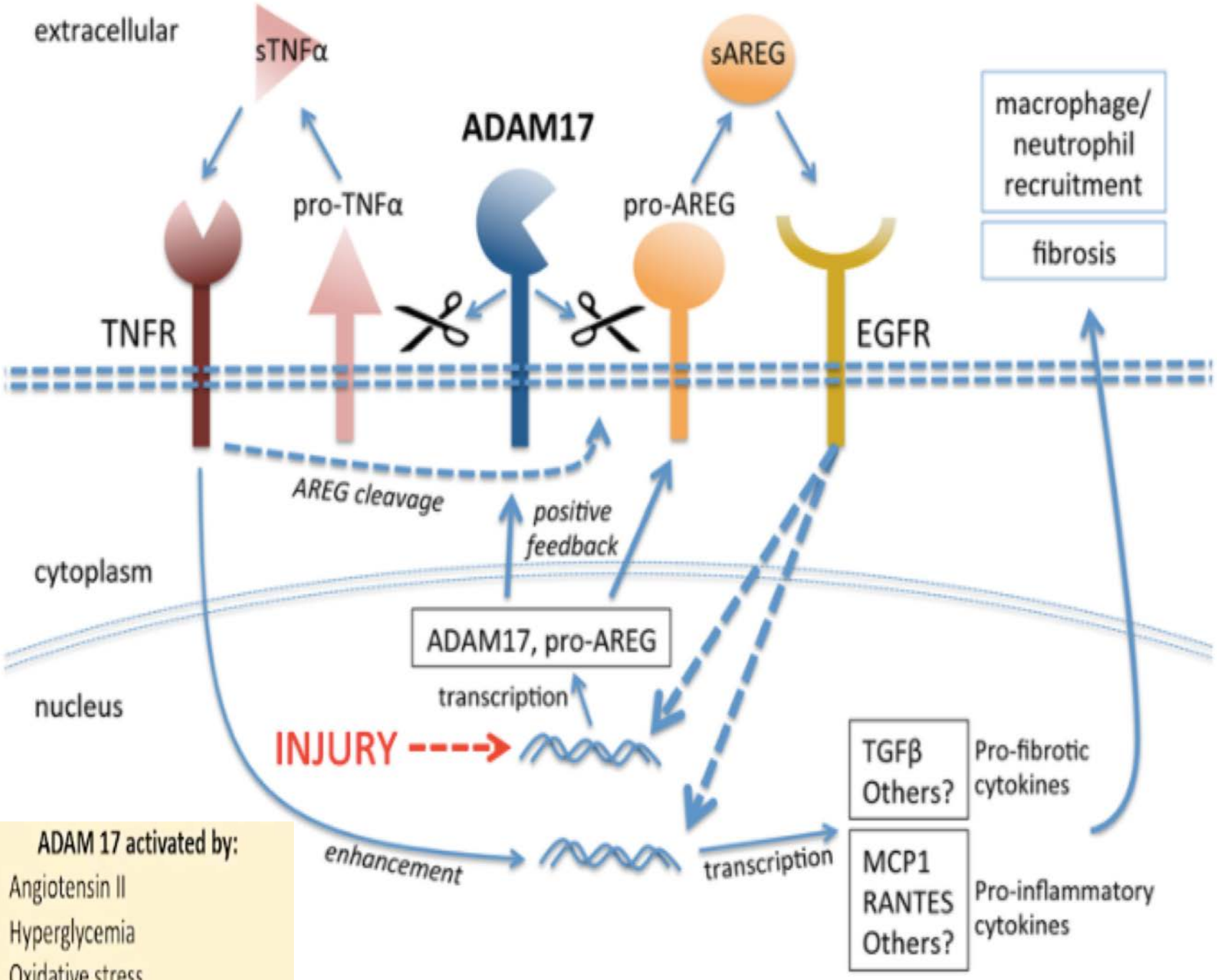
ADAM 17
METALLOPROTEINASE
is a key component of ACE2 modulation and plays a complex role in inflammation and immunosurveillance

ACTIVATION
EQUALS
ADDITIONAL INSULT

UNCHECKED INFLAMMATION

……

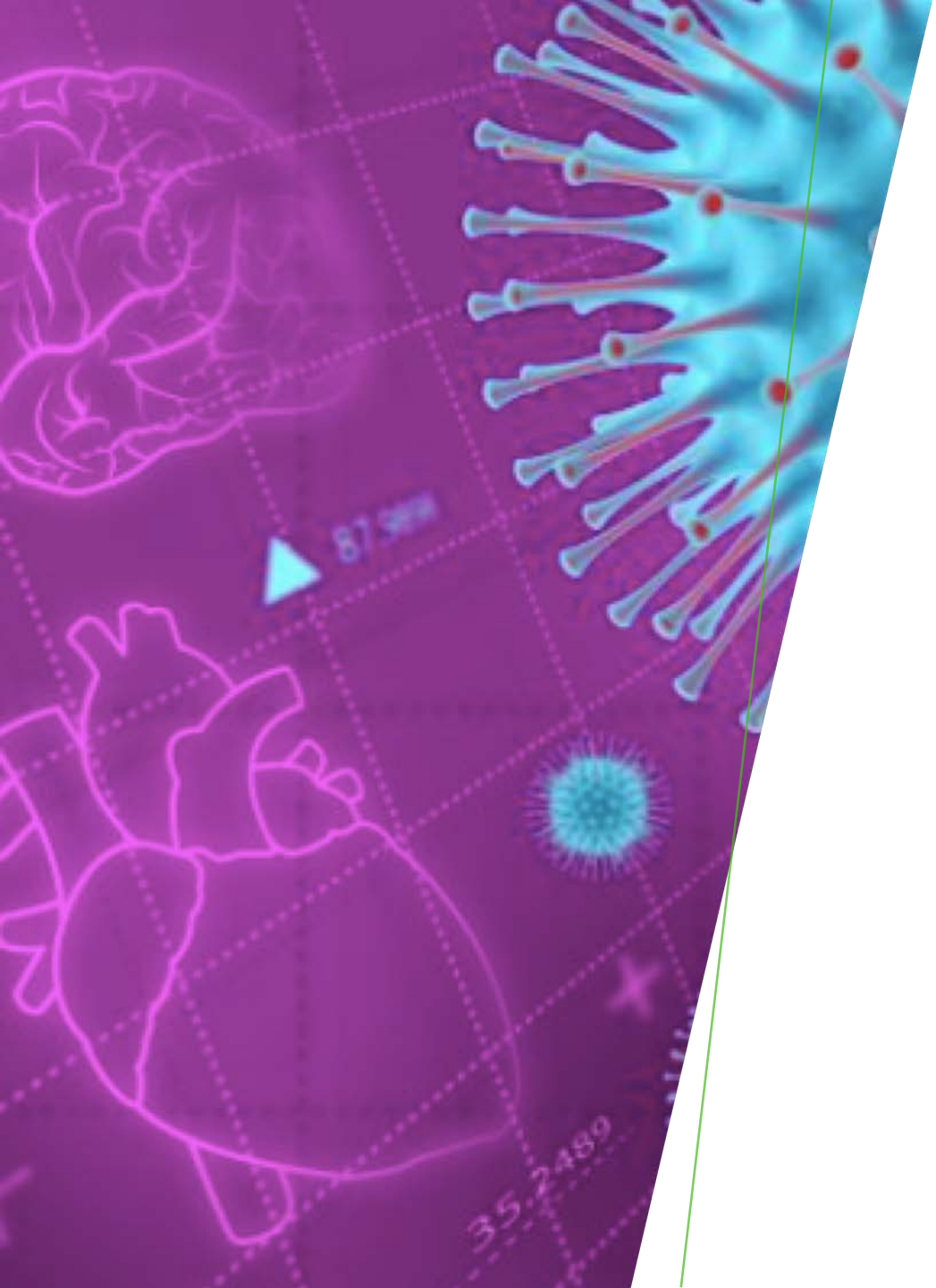
BEGETS MORE INFLAMMATION



INFECTION WITH SARS-COV-2 LEADS TO AN INCREASE IN ADAM17 ACTIVITY CONTRIBUTING TO A MACROPHAGE PREDOMINANT INFLAMMATORY RESPONSE, DIMINISHED IMMUNOSURVEILLANCE AND DECREASED VIRAL CLEARANCE.

DATA SUGGESTS SEVERE LUNG INJURY IN COVID-19 IS ASSOCIATED WITH HIGHER LEVELS OF TNF-, IL-6, T-CELL LYMPHOPENIA, HYPERCOAGULABILITY, AND A MACROPHAGE-PREDOMINANT IMMUNE RESPONSE.

THIS CLINICAL PICTURE IS CONSISTENT WITH DYSREGULATION OF MANY OF THE MOLECULAR PATHWAYS IN WHICH ADAM17 PARTICIPATES



PATHOLOGY

LUNGS = MOST VULNERABLE ORGAN

DUE TO THE HIGH PERCENTAGE OF ACE2 EXPRESSING CELLS

83% OF ACE2 EXPRESSING CELLS IN THE LUNGS PRODUCE SURFACTANT:

SURFACTANT REDUCES SURFACE TENSION

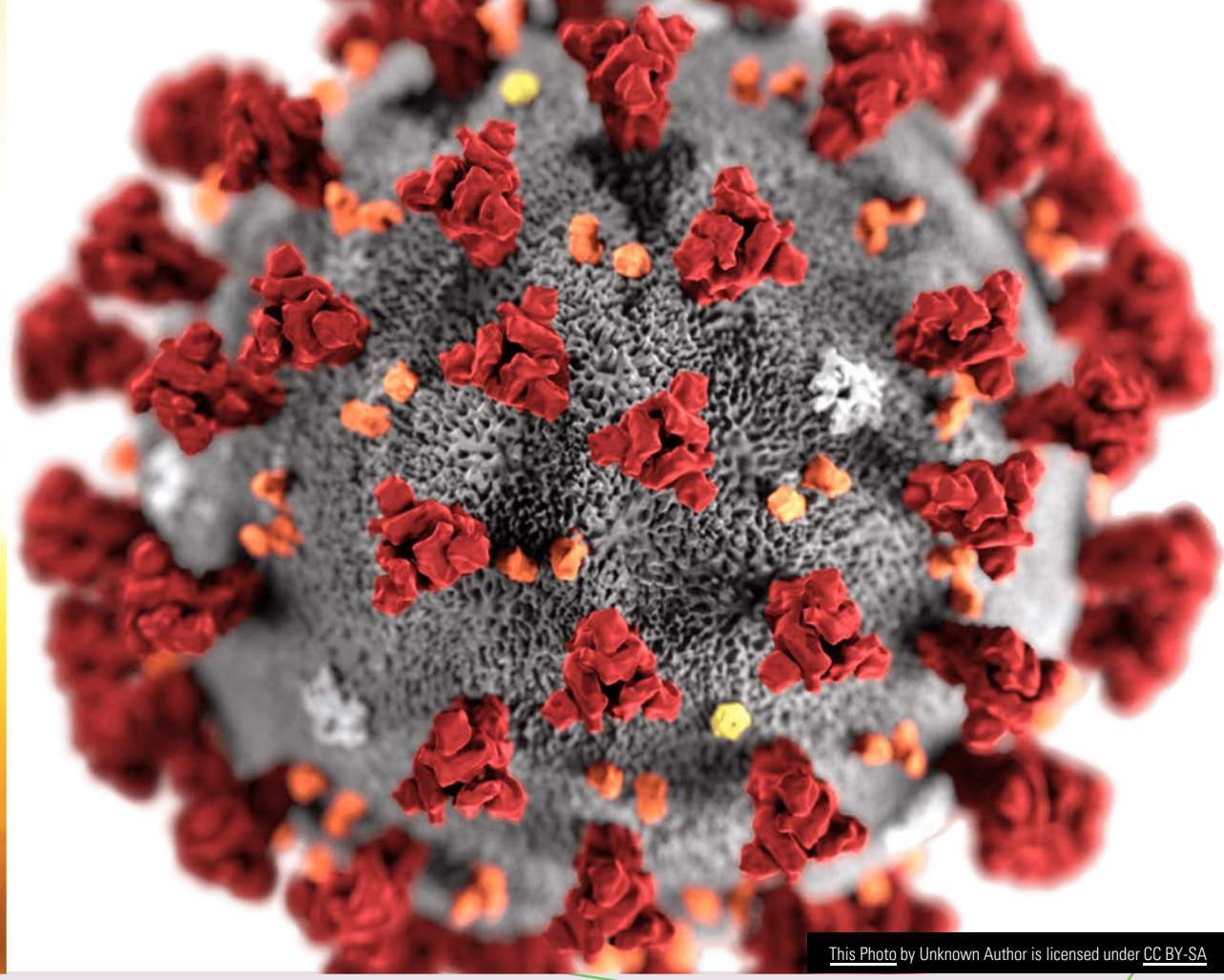
WITHOUT SURFACTANT THE ALVEOLI BECOME STICKY
02 EXCHANGE CANNOT OCCUR

YOUR LUNGS CANNOT EXPAND PROPERLY
YOU CANNOT EXCHANGE GAS ADEQUATELY,
AND YOU BECOME HYPOXIC

ACE2 RECEPTORS

ALSO FOUND IN HEART,

LINING OF VESSELS AND GI



BUT IT IS NOT ALL ABOUT THE VIRUS:

A CHANGE IN SETTING OR CONTEXT, CAN CHANGE THE STORY

THE HOST HEALTH AND HOST RESPONSE DETERMINES OUTCOME

The Functional Medicine Model

The Functional Medicine model is an individualized, patient-centered, science-based approach that identifies and addresses the underlying causes of disease and promotes optimal wellness.

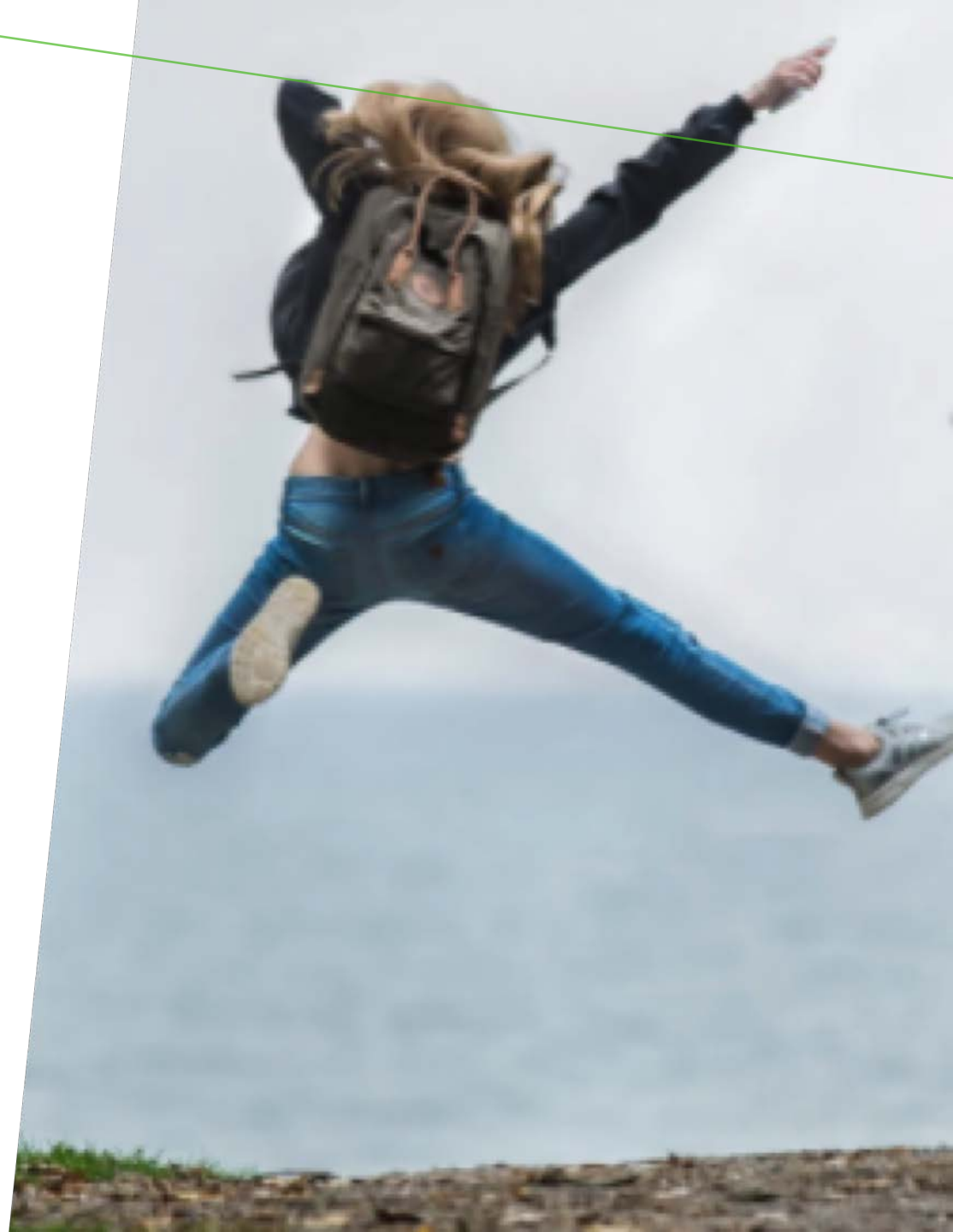
It utilizes a detailed understanding of each patient's genetic, biochemical, and lifestyle factors and leverages that data to direct personalized treatment plans that lead to improved patient outcomes.

The Institute for Functional Medicine. 2020. *Functional Medicine | IFM*. [online] Available at: <https://www.ifm.org/functional-medicine/> [Accessed 18 September 2020]

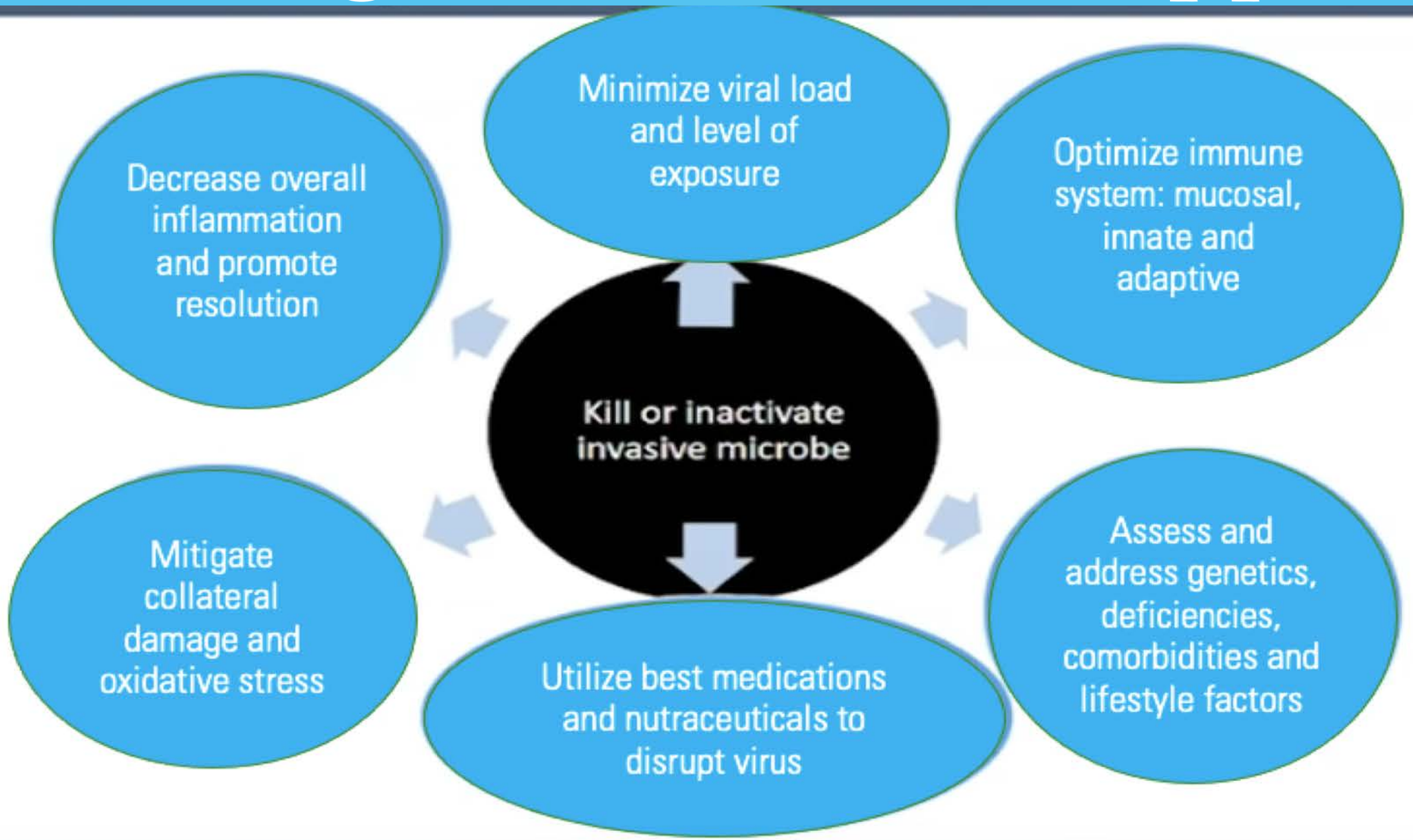
THE HEALTH OF THE HOST, IN LARGE PART, DETERMINES THE SEVERITY OF SYMPTOMS AND THE MANIFESTATIONS OF DISEASE

THE PUTATIVE ROLE OF PREEXISTING FUNCTIONAL IMBALANCES:

- *MITOCHONDRIAL FUNCTION/DYSFUNCTION*
- *OXIDATIVE STRESS*
- *HYPERGLYCEMIA*
- *INFLAMMATION*
- *IMMUNE SYSTEM FUNCTION/DYSFUNCTION*



Strategies and overall Approach



GENETIC VARIANTS

ANOTHER REASON WHY SOME GET SICK, AND OTHERS DO NOT

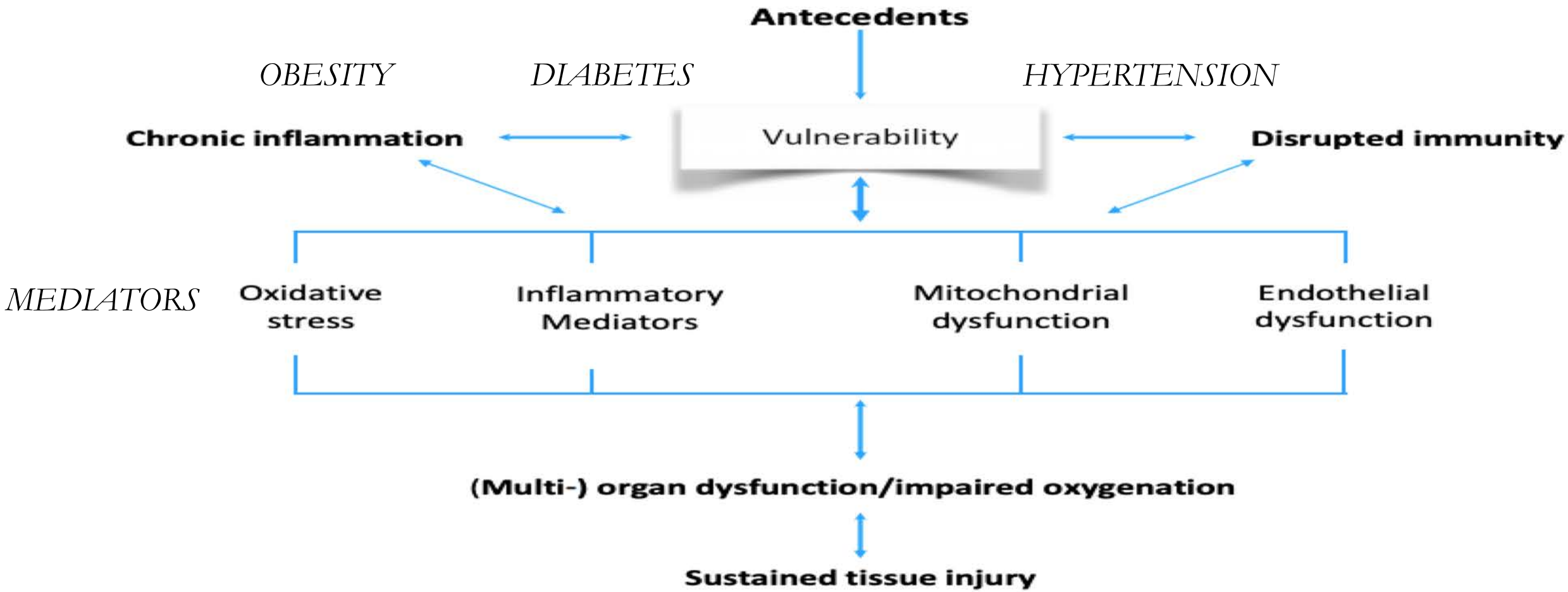
* APOE4 = 4 X MORTALITY RISK, AND 2.24 X POSITIVITY RATE

* TMPRSS2 ENZYME SNPS (INVOLVED IN CLEAVAGE AND VIRAL BINDING)

* ACE2 RECEPTOR SNPS AND RECEPTOR VARIABILITY

- ApoE4
  - *ApoE* e4e4 genotype was associated with increased risks of ***test positivity*** (OR = **2.24**, 95% CI: 1.72–2.93, $p = 3.24 \times 10–9$) and of ***mortality*** with test-confirmed COVID-19 (OR = **4.29**, 95% CI: 2.38–7.72, $p = 1.22 \times 10–6$), compared to e3e3s.
    - Kuo CL, Pilling LC, Atkins JL, et al. ApoE e4e4 genotype and mortality with COVID-19 in UK Biobank [published online ahead of print, 2020 Jul 4]. *J Gerontol A Biol Sci Med Sci*. 2020;glaa169. doi:10.1093/gerona/glaa169

THE ENVIRONMENT: AND THAT WHICH MAKES US VULNERABLE



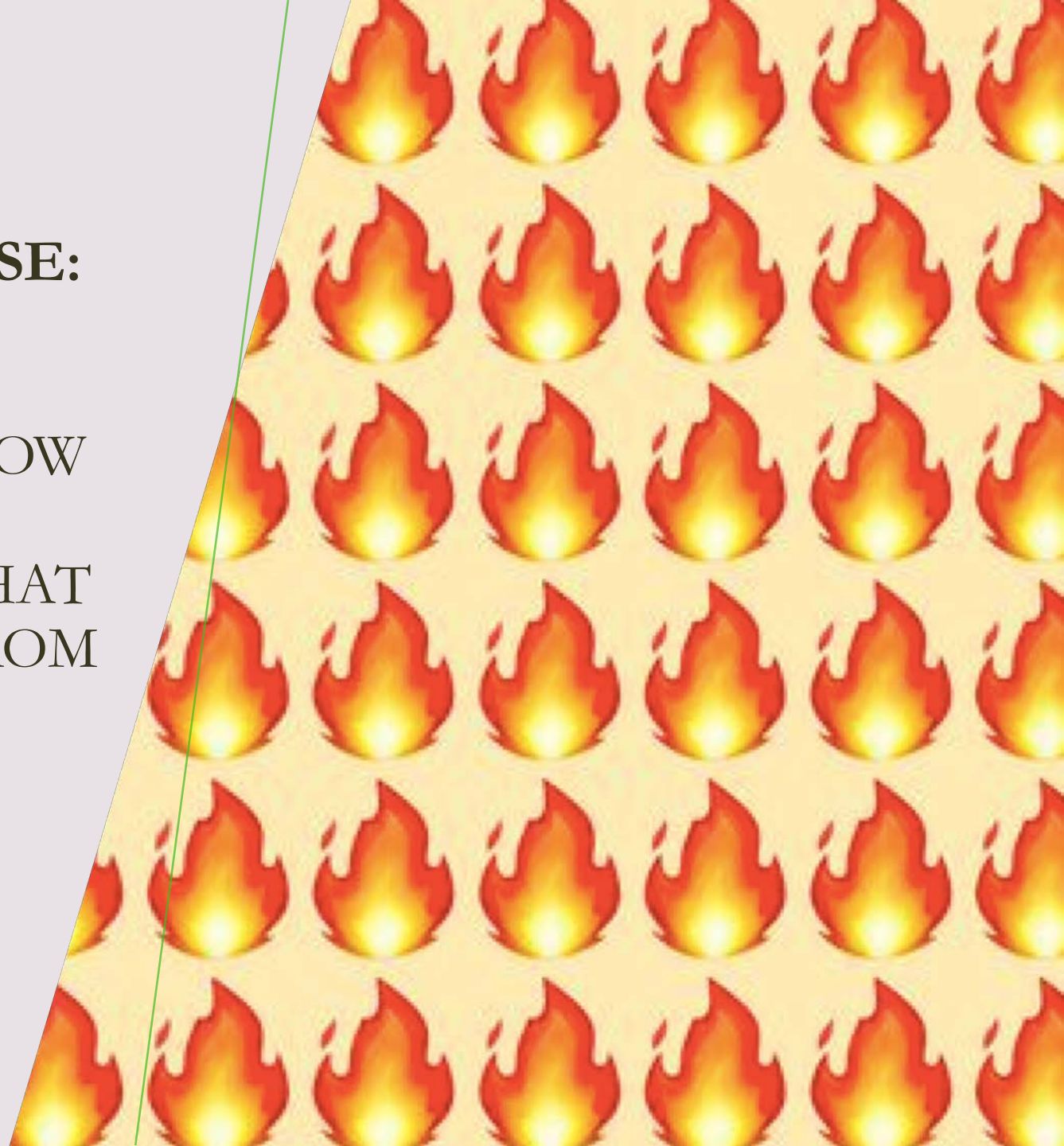
Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci Rev*. 2020;nwaa041. Published 2020 Mar 13. doi:10.1093/nsr/nwaa041
Schönrich G, Raftery MJ, Samstag Y. Devilishly radical NETwork in COVID-19: Oxidative stress, neutrophil extracellular traps (NETs), and T cell suppression. *Adv Biol Regul*. 2020;77:100741. doi:10.1016/j.jbior.2020.100741
Saleh J, Peyssonnaux C, Singh KK, Edeas M. Mitochondria and microbiota dysfunction in COVID-19 pathogenesis [published online ahead of print, 2020 Jun 20]. *Mitochondrion*. 2020;54:1-7. doi:10.1016/j.mito.2020.06.008
Nishiga, M., Wang, D.W., Han, Y. et al. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 17, 543–558 (2020). https://doi.org/10.1038/s41569-020-0413-9


HOW CAN FUNCTIONAL
MEDICINE STRENGTHEN
THE FOUNDATION?

INFLAMMATION
CAUSES
IMPAIRED HOST VIRAL DEFENSE:

THE PROBLEM IN DEFENSE IS HOW FAR YOU CAN GO WITHOUT "DESTROYING FROM WITHIN, WHAT YOU ARE TRYING TO DEFEND FROM WITHOUT."

DWIGHT EISENHOWER



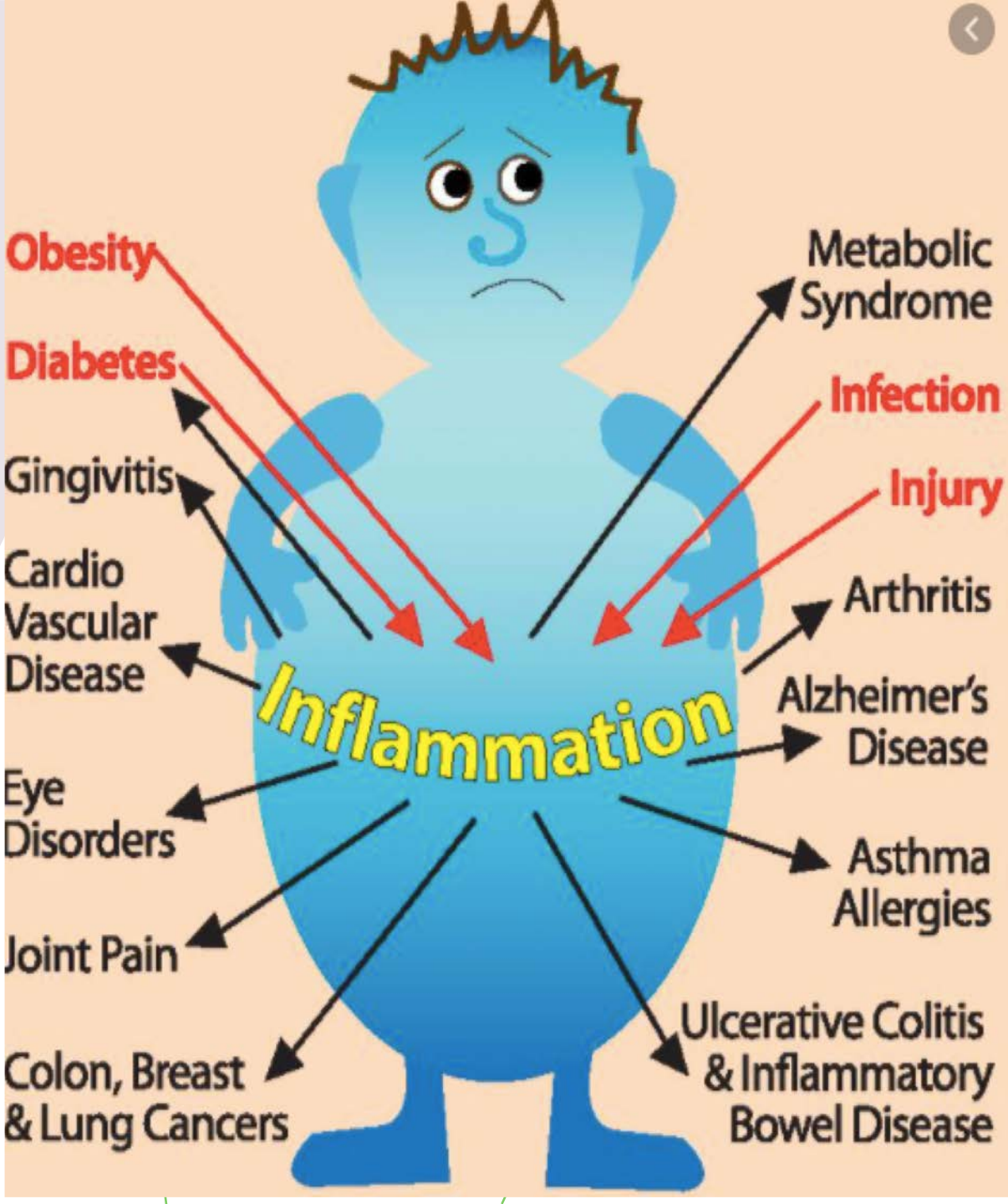
ROLE OF PRE-EXISTING INFLAMMATION

INFLAMMATION IS HOW THE BODY RESPONDS TO VIRAL INFECTION

CHRONIC INFLAMMATION IS ASSOCIATED WITH INCREASED ANGIOTENSIN AND LOWERED ACE2 AT BASELINE

THE CYTOKINE STORM, AN EXAGGERATED INFLAMMATORY RESPONSE, IS PARTLY RESPONSIBLE FOR SEVERE MORBIDITY AND MORTALITY IN COVID-19

COVID-19 REINFORCES THIS PATHWAY INCREASED COLLATERAL DAMAGE OCCURS



ADDITIONAL CONSEQUENCES OF INFLAMMATION

PRO-INFLAMMATORY MEDIATORS SUCH AS TNF-A AND NFK-B INCREASE EXPRESSION OF BRADYKININ

BRADYKININ IS A PROINFLAMMATORY PEPTIDE THAT ACTS AS A VASODILATOR.

BRADYKININ CAUSES:

PROPAGATION OF INFLAMMATION, VASODILATION, INCREASED VASCULAR PERMEABILITY, RELEASE OF INFLAMMATORY MEDIATORS = FURTHER DAMAGE

HYPERGLYCEMIA CAUSES
IMPAIRED HOST VIRAL DEFENSE:

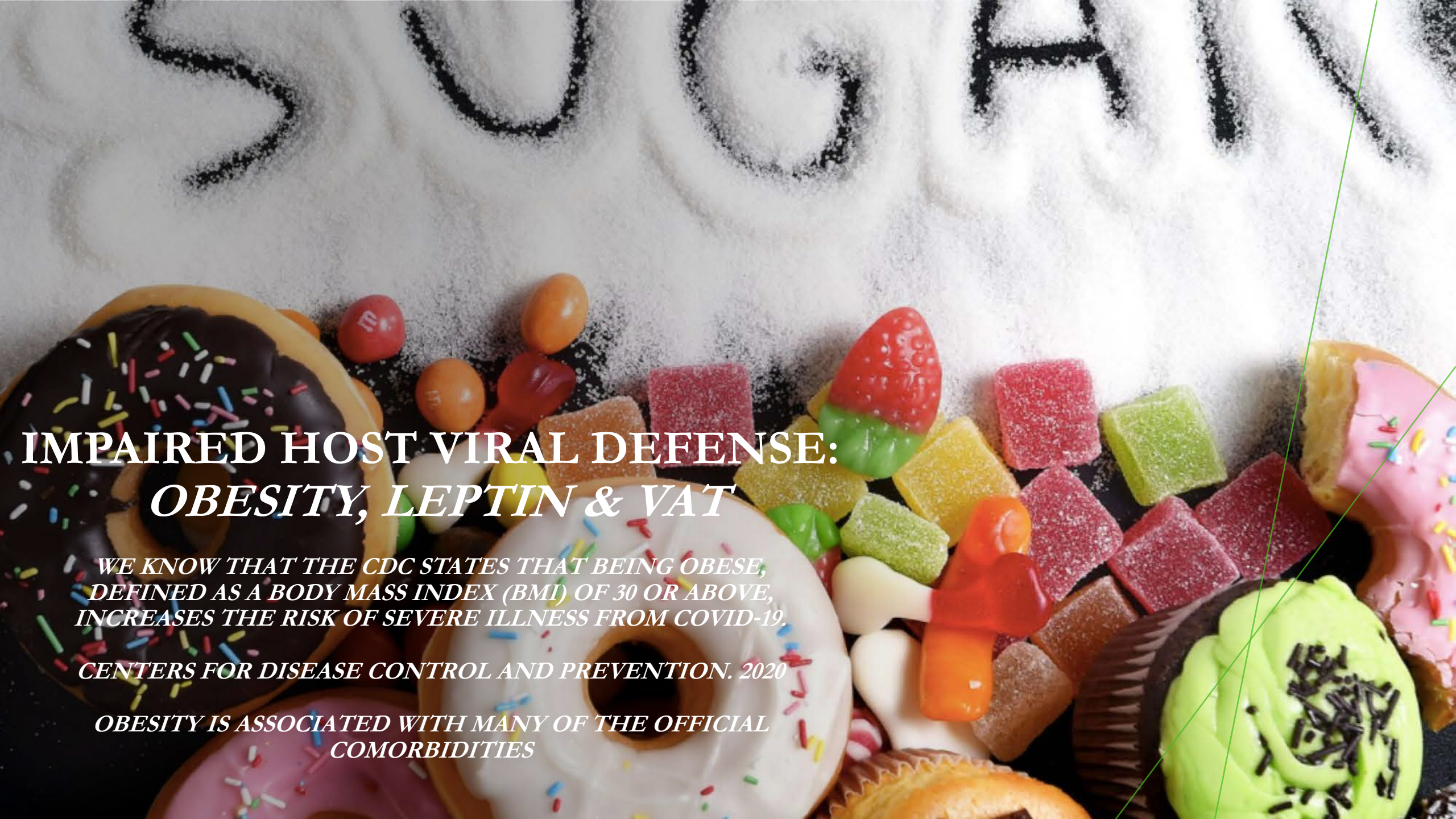
DIABETICS HAVE INCREASED SEVERITY OF COVID-19

REASONS INCLUDE:

- *ELEVATED FURIN = INCREASED VIRAL DOCKING*
- *GLUTATHIONE DEPLETION DUE TO OXIDATIVE STRESS*
- *NADPH DEPLETION BY NADPH OXIDASE2*
- *INCREASED SUSCEPTIBILITY AND ADVERSE OUTCOMES FROM VIRAL INFECTIONS ATTRIBUTED TO A COMBINATION OF DYSREGULATED INNATE IMMUNITY AND MALADAPTIVE INFLAMMATORY RESPONSES*
- *EFFECT ON ACE-2 RECEPTORS*
- *ROLE OF ADAM-17 ENZYME*
- *INCREASE IN PLASMIN*
- *INCREASE IN PROINFLAMMATORY CYTOKINES.*
- *MELATONIN RECEPTOR FUNCTION (DECREASED)*
- *ALDOSE REDUCTASE (OX STRESS, AGES, INFLAMMATION)*

IN THE SETTING OF METABOLIC SYNDROME, ADIPOSE TISSUE BECOMES A SIGNIFICANT STORAGE SITE FOR INFLAMMATORY CYTOKINES. INFLAMMATORY CYTOKINES STIMULATE BRADYKININ WHICH WORSENS THE COURSE

HITS MULTIPLE PATHWAYS AT ONCE



IMPAIRED HOST VIRAL DEFENSE:
OBESITY, LEPTIN & VAT

WE KNOW THAT THE CDC STATES THAT BEING OBESE, DEFINED AS A BODY MASS INDEX (BMI) OF 30 OR ABOVE, INCREASES THE RISK OF SEVERE ILLNESS FROM COVID-19.

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2020

OBESITY IS ASSOCIATED WITH MANY OF THE OFFICIAL COMORBIDITIES

OBESITY IS ASSOCIATED WITH MANY OF THE UNDERLYING IMBALANCES THAT INCREASE HOST VULNERABILITIES

- *INFLAMMATION*
- *OXIDATIVE STRESS*
- *ELEVATED FURIN*
- *ELEVATED LEPTIN*
- *VAT (VISCERAL ADIPOSE TISSUE)*

IS LEPTIN THE LINK?

Obesity, (and diabetes) are the most common comorbidities in SARS-CoV-2

Elevated leptin and insulin resistance are hallmarks of obesity.

* Leptin also modulates T cell number and function

Leptin connects metabolism with the immune response.

Leptin dysregulation has serious consequences during an infection.

Leptin, is involved in weight regulation, also plays a role in the modulation of the innate and adaptive immune system by activating neutrophils, macrophages and T lymphocytes.

COVID-19 survival rates have improved in obese mice treated with anti-leptin antibodies

Chua MWJ, Zheng S. Obesity and COVID-19: The clash of two pandemics [published online ahead of print, 2020 Jun 25]. Obes Res Clin Pract. 2020;14(4):380-382. doi:10.1016/j.orcp.2020.06.003

MITOCHONDRIAL DYSFUNCTION CAUSES

IMPAIRED HOST VIRAL DEFENSE:

- *MITOCHONDRIA HAVE ANTI-VIRAL FUNCTION.*

- *MITOCHONDRIA WORK AT LEVEL OF INNATE IMMUNE SYSTEM AFTER RECOGNITION OF PAMP'S (PATHOGENS) BY TOLL LIKE RECEPTORS TO ACTIVATE GENES TO MAKE PROTEINS TO DESTROY VIRUSES.*

- *MITOCHONDRIAL ANTIVIRAL SIGNALING (MAVS) PROTEIN COORDINATES ACTIVATION OF INTERFERON AND AUTOPHAGY (CELL DEATH).*

- *MAVS PROTEIN INTERACTS WITH THE ACTIVE FORM OF THE NLRP3 INFLAMMASOME INSIDE THE MITOCHONDRIA*

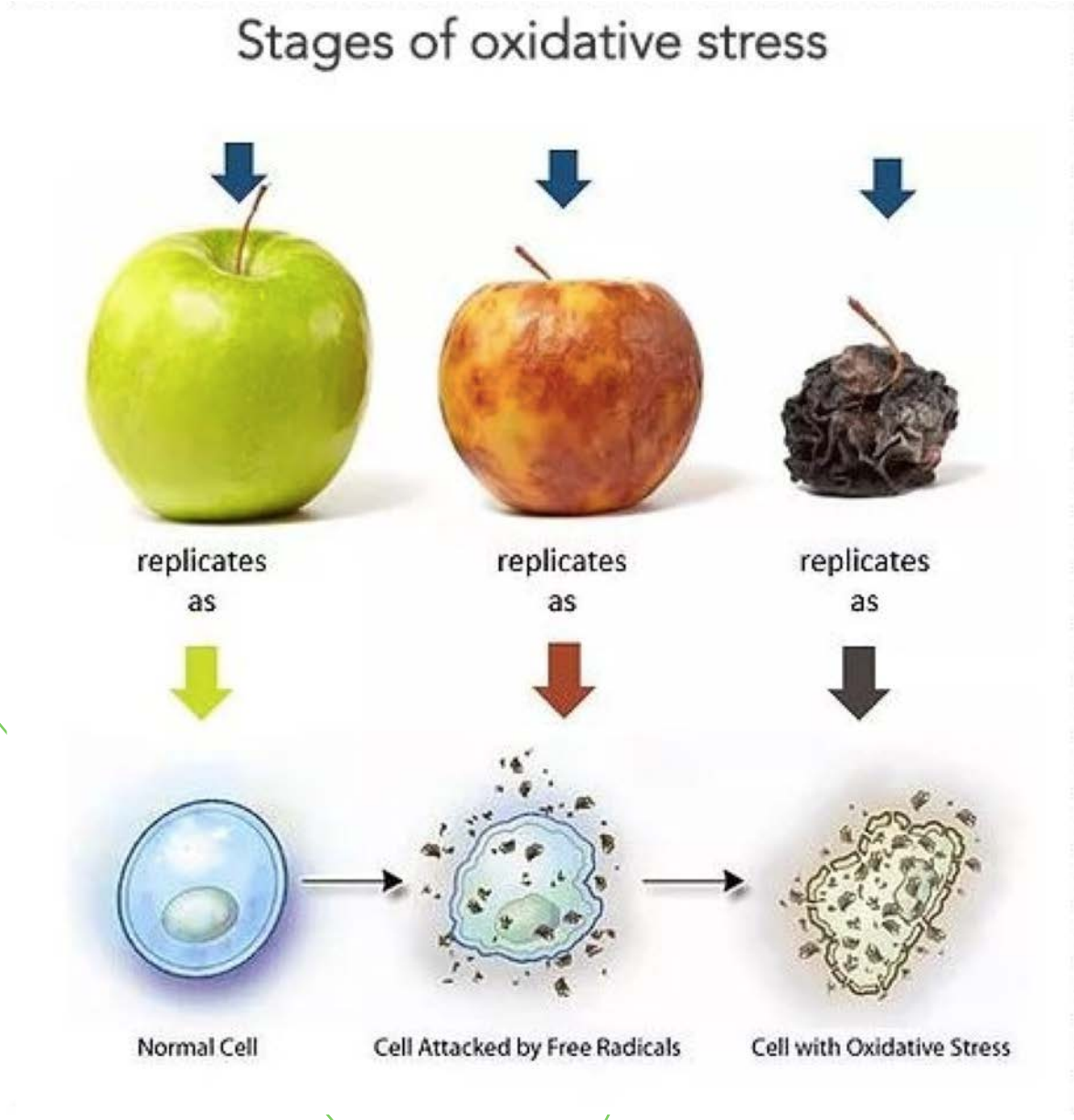
SARS-COV-2 CAUSES MITOCHONDRIAL DYSFUNCTION

- *SARS-COV HAS BEEN RECOGNIZED TO MANIPULATE HOST CELL MITOCHONDRIA AND TO DAMAGE MITOCHONDRIAL FUNCTION*

- *SARS-COV2 TARGETS THE MAVS PROTEIN (ANTIVIRAL FXN) WHICH SUPPRESSES ANTIVIRAL CELLULAR SIGNALING*

IMPAIRED HOST VIRAL DEFENSE:

OXIDATIVE STRESS



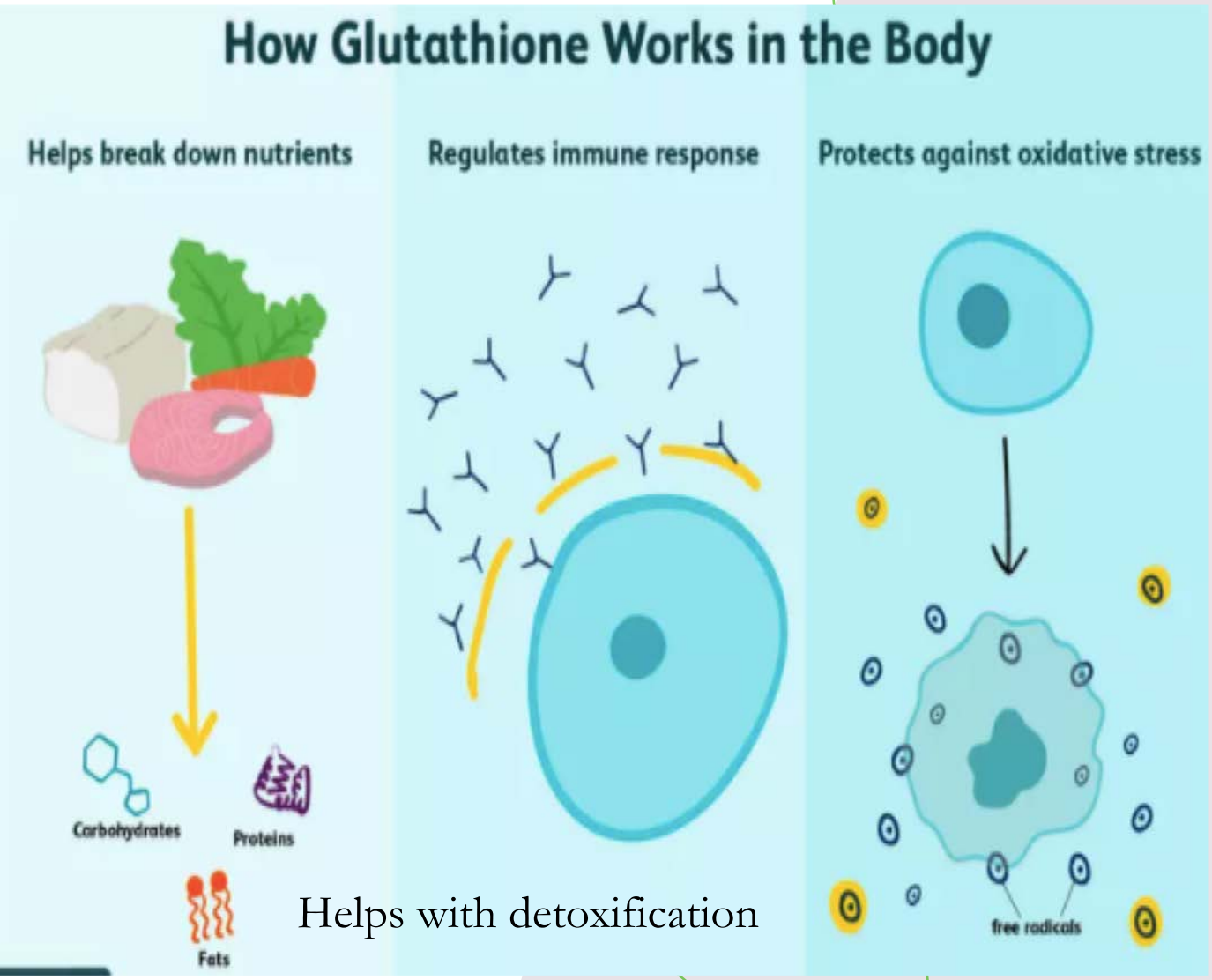
OXIDATIVE STRESS IS A KEY PLAYER IN SEVERE ACUTE RESPIRATORY SYNDROME (ARDS) FROM CORONAVIRUS (SARS-COV2) INFECTION

1.) BI-DIRECTIONAL ROS FORMATION AND OXIDATIVE CELLULAR DAMAGE IS A COMMON RESPONSE TO VIRAL EXPOSURE

2.) OVERPRODUCTION OF ROS AND A DEPLETED ANTIOXIDANT CAPACITY CONTRIBUTES TO THE PATHOGENESIS OF MORE SEVERE SARS-COV2 INFECTION

WHAT YOU COME TO THE TABLE WITH EFFECTS YOUR OUTCOME
"HOW FULL IS YOUR WATER BUCKET??"

Glutathione may be a critical link



Helps with detoxification

STUDY IDENTIFIED DEFICIENCY OF GLUTATHIONE AS THE MOST LIKELY CAUSE OF SERIOUS MANIFESTATIONS AND DEATH IN COVID-19 PATIENTS

THE HYPOTHESIS THAT GLUTATHIONE DEFICIENCY IS THE MOST PLAUSIBLE EXPLANATION FOR SERIOUS MANIFESTATION AND DEATH IN COVID -19 PATIENTS WAS PROPOSED BASED ON AN EXHAUSTIVE LITERATURE ANALYSIS AND OBSERVATIONS.

ENDOGENOUS GLUTATHIONE DEFICIENCY IS A CRUCIAL FACTOR ENHANCING SARS -COV - 2 -INDUCED OXIDATIVE DAMAGE OF THE LUNG. AS A RESULT, LEADS TO SERIOUS MANIFESTATIONS, SUCH AS ACUTE RESPIRATORY DISTRESS SYNDROME, MULTIORGAN FAILURE, AND DEATH IN COVID -19 PATIENTS.

WHEN THE ANTIVIRAL ACTIVITY OF GSH IS CONSIDERED, INDIVIDUALS WITH GLUTATHIONE DEFICIENCY SEEM TO HAVE A HIGHER SUSCEPTIBILITY FOR UNCONTROLLED REPLICATION OF SARS-COV - 2 VIRUS AND THEREBY SUFFER FROM AN INCREASING VIRAL LOAD. THE SEVERITY OF CLINICAL MANIFESTATIONS IN COVID -19 PATIENTS IS DETERMINED BY THE DEGREE OF IMPAIRED REDOX HOMEOSTASIS ATTRIBUTABLE TO THE DEFICIENCY OF REDUCED GLUTATHIONE AND INCREASED ROS PRODUCTION.

POLONIKOV A. ENDOGENOUS DEFICIENCY OF GLUTATHIONE AS THE MOST LIKELY CAUSE OF SERIOUS MANIFESTATIONS AND DEATH IN COVID-19 PATIENTS.

ACS INFECT DIS. 2020;6(7):1558-1562. DOI:10.1021/ACSINFECDIS.0C00288

UNDERSTANDING THE HOST IMMUNE SYSTEM AND THE COURSE OF THE VIRUS

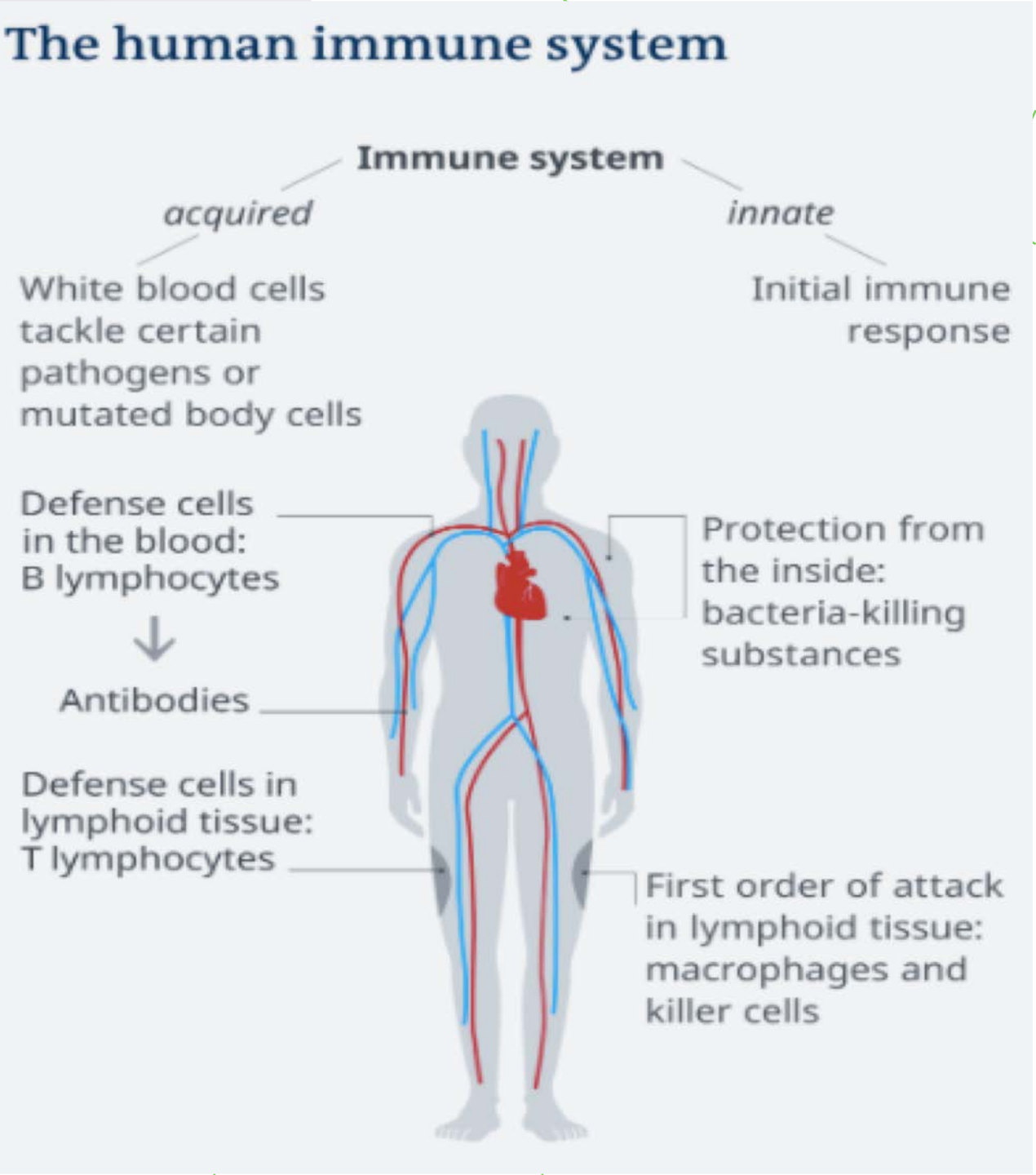
IMMUNE SYSTEM

HOST *DEFENSE*

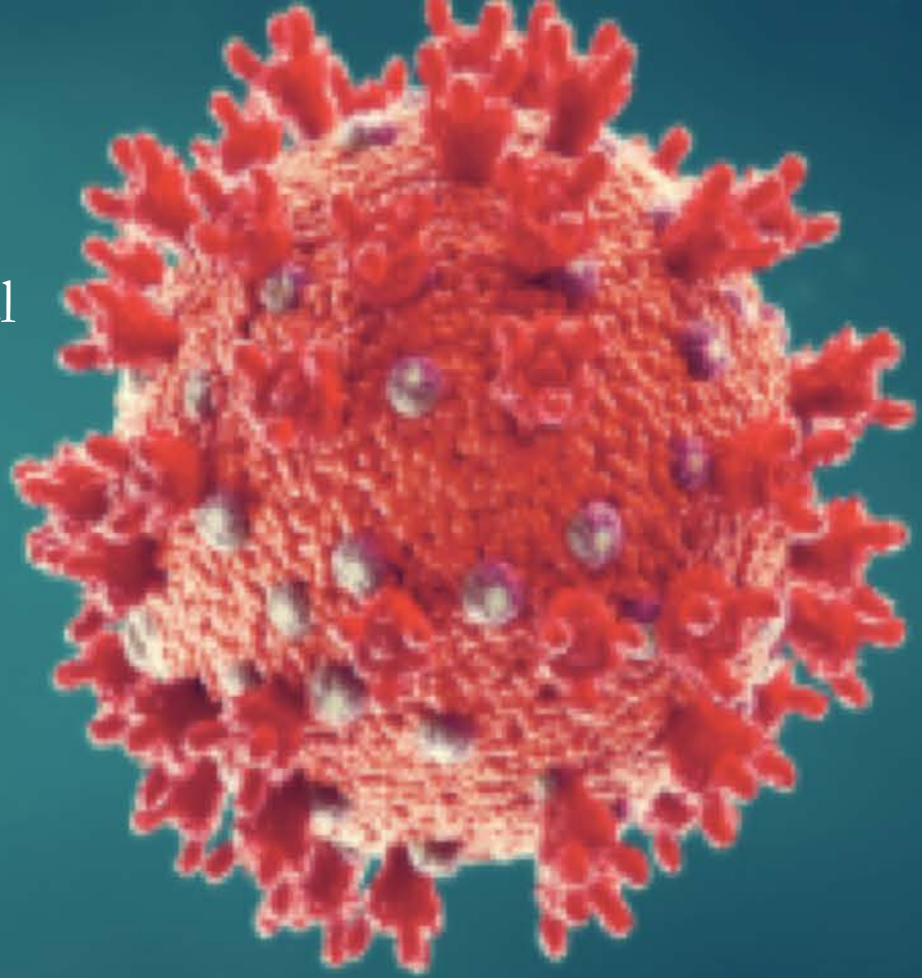
IMMUNE SYSTEM WORKS IN LAYERS OF INCREASING SPECIFICITY:

THERE CAN BE BREAKDOWN AT ANY LEVEL

- *MUCOSAL IMMUNE SYSTEM*
- *INNATE IMMUNE SYSTEM*
- *ADAPTIVE IMMUNE SYSTEM*

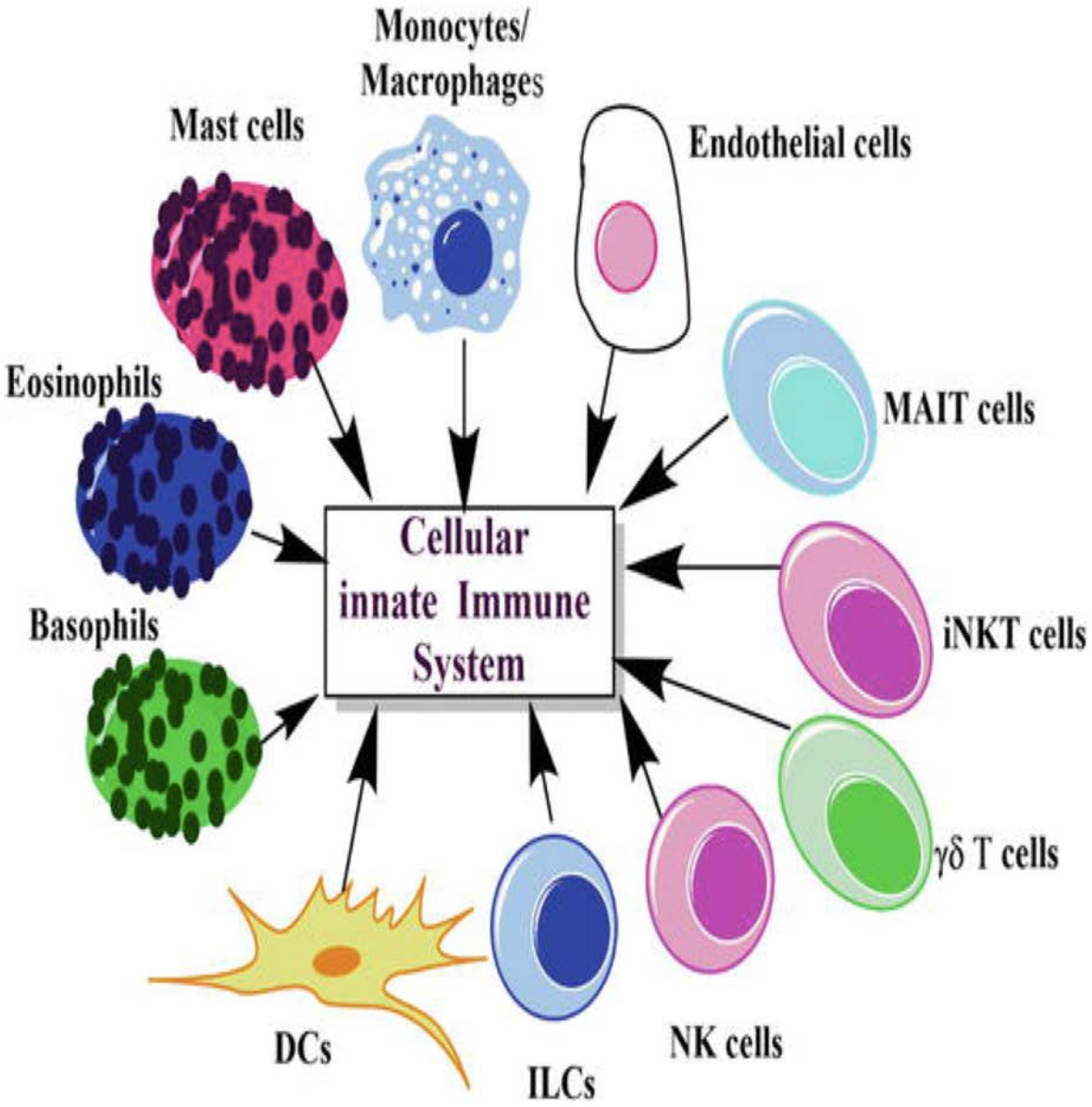


Many, if not all, viruses…suppress the innate immune responses to gain a window of opportunity for efficient viral replication, and perpetuation of infection.



THE HOST'S IMMUNE RESPONSE IS OFTEN INCOMPLETE, DELAYED OR DIMINISHED;
AND THE DISPLAYS AN OVERLY STRONG INDUCTION
(AFTER THE INITIAL DELAY)
THE CONSEQUENCE IS COLLATERAL TISSUE DAMAGE

KIKKERT M. INNATE IMMUNE EVASION BY HUMAN RESPIRATORY RNA VIRUSES.
J INNATE IMMUN. 2020;12(1):4-20. DOI:10.1159/000503030



DAYS 0 – 5:

- KEY COMPONENTS OF THE HOST IMMUNE RESPONSE IN THE PRE-SYMPTOMATIC STAGE

- MUCOSAL & INNATE IMMUNE SYSTEM
- SECRETORY IgA
- INFLAMMASOMES
- CYTOKINES
- NK CELLS
- GUT MICROBIOTA

DAYS 5 - 12:

HOST IMMUNE RESPONSE

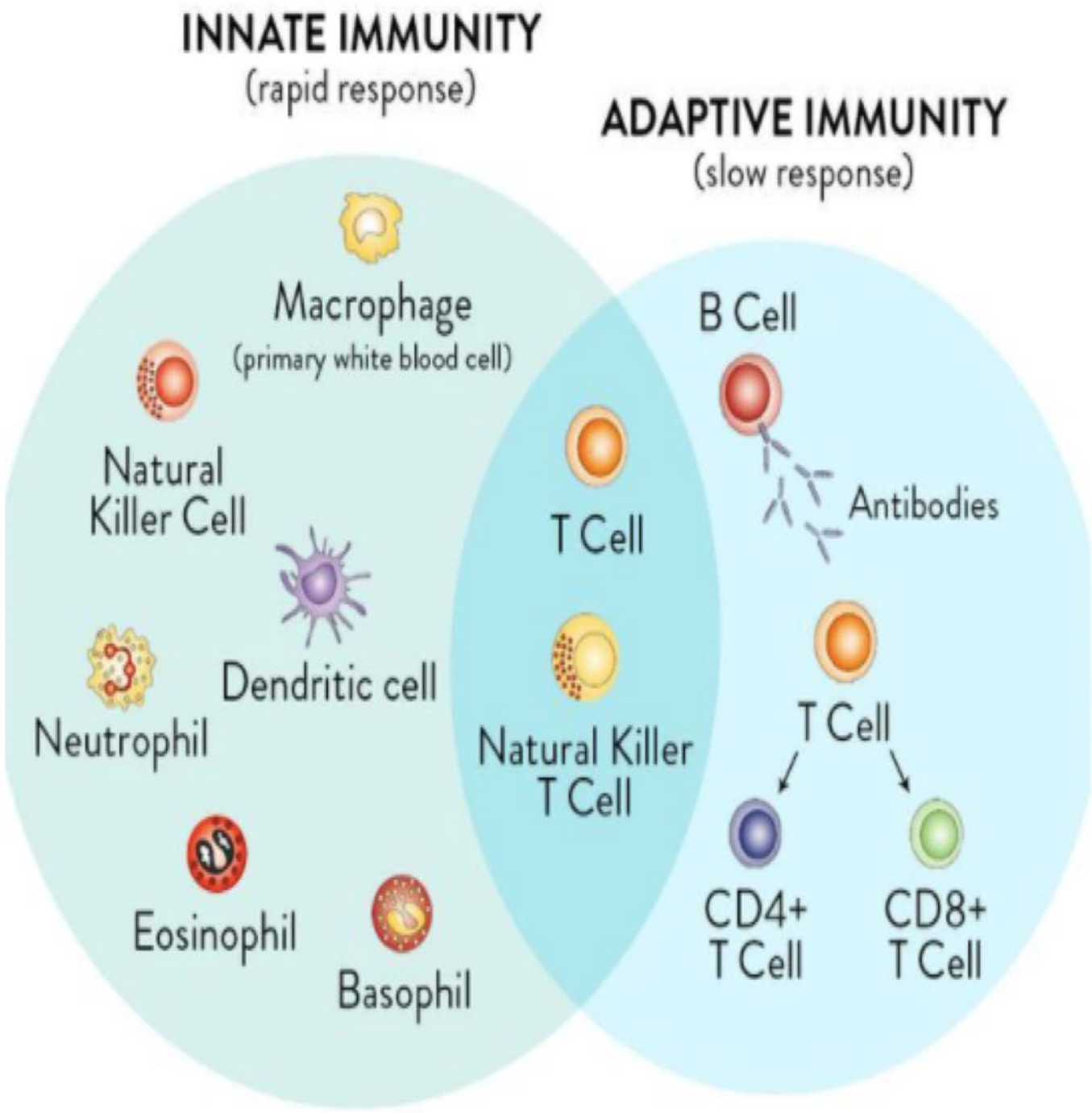
EARLY INFECTION:

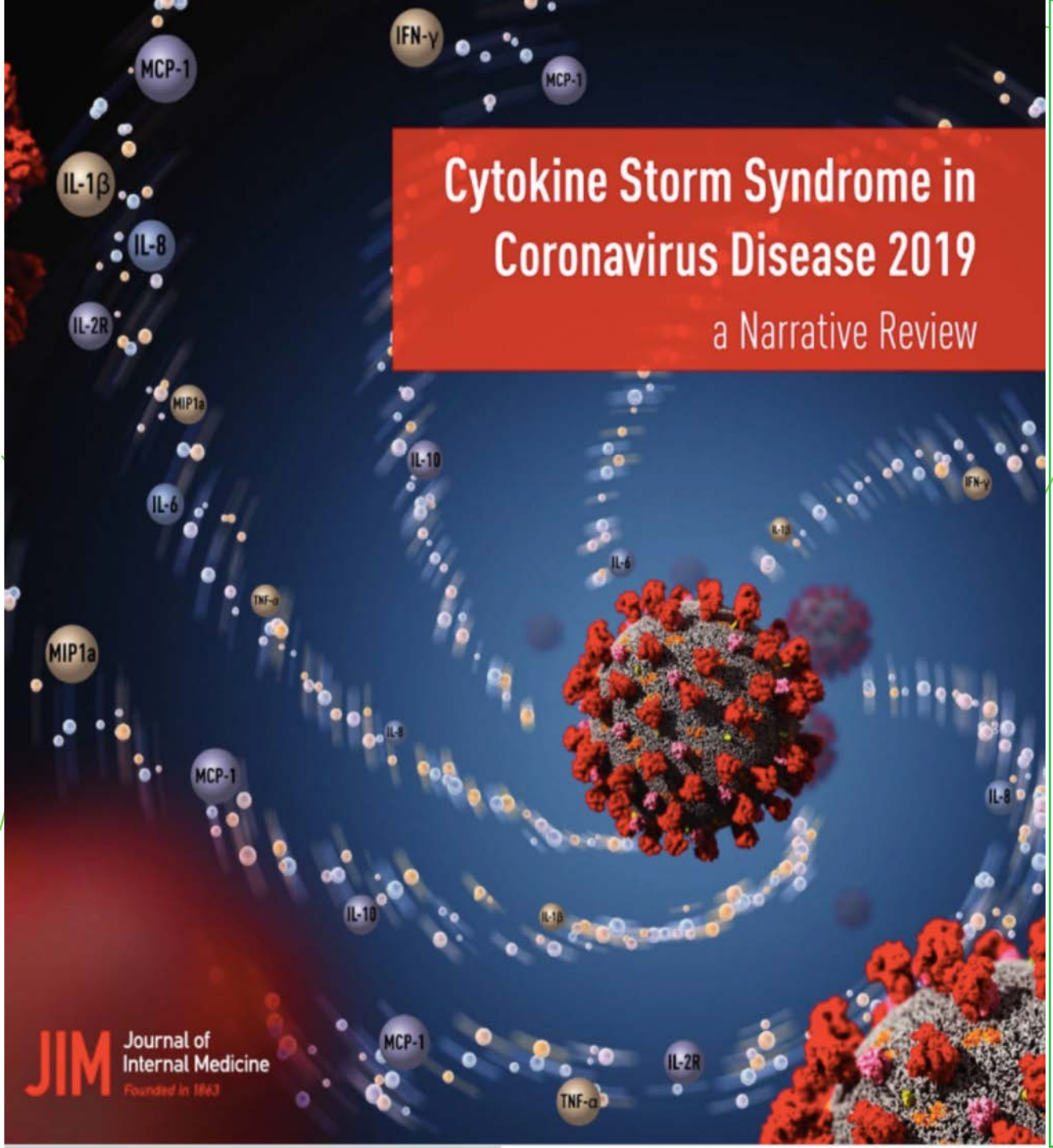
MILD TO MODERATE SYMPTOMS

INNATE AND ADAPTIVE

IMMUNE SYSTEM

- *INFLAMMASOMES*
- *CYTOKINES – KININS? – BRADYKININ?*
- *NK CELLS*
- *(GUT MICROBIOTA)*
- *IgM •IgG*





DAYS 12 AND BEYOND:

HOST IMMUNE RESPONSE
CAN GO 1 OF 2 WAYS

1.) RECOVERY
OR
2.) SEVERE ILLNESS AND HOSPITALIZATION

VULNERABILITY IS INFLUENCED BY:

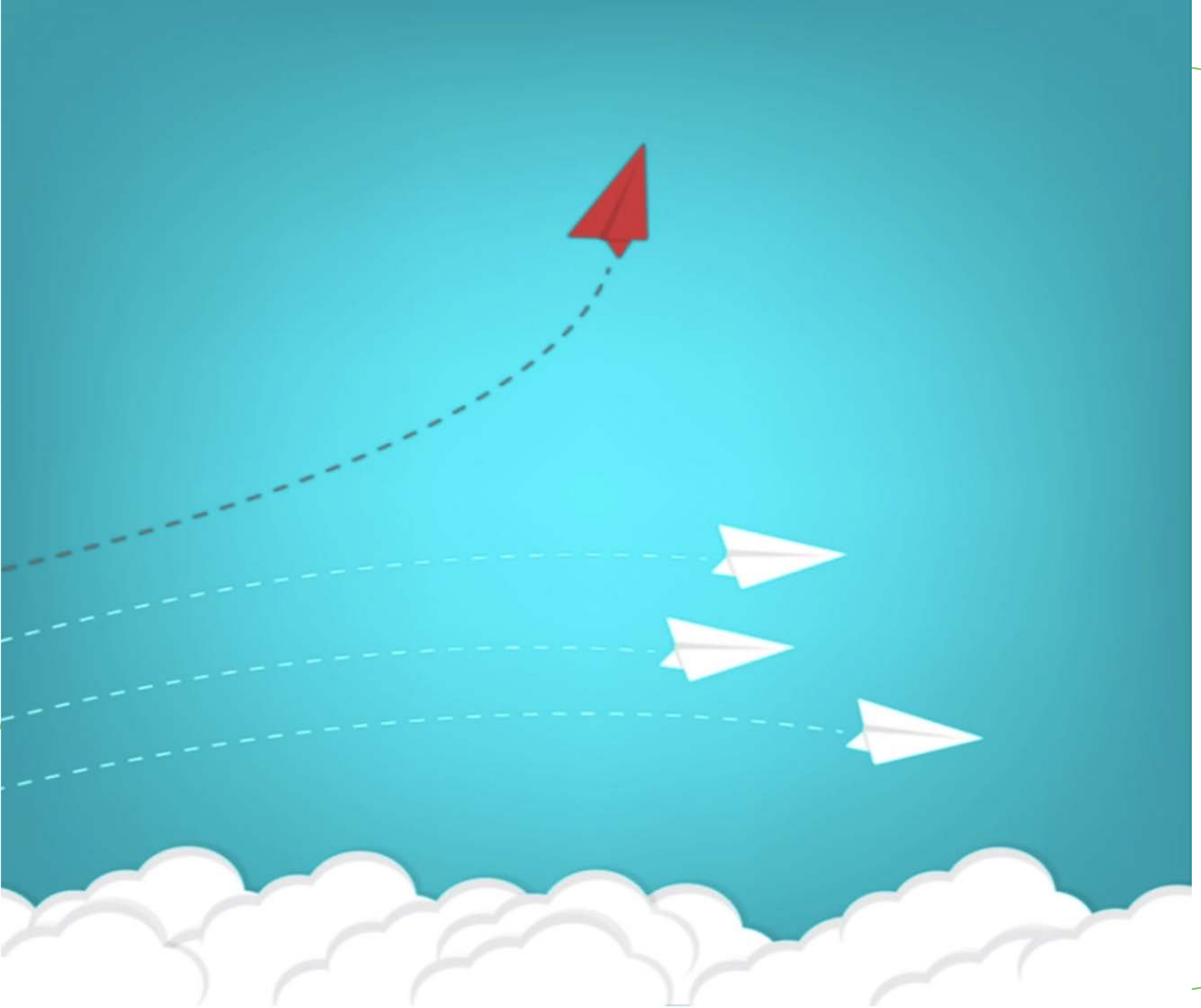
- *PRE-EXISTING COMORBID CONDITIONS*

- *LEVEL OF FUNCTION OF IMMUNE SYSTEM FROM PRE-EXPOSURE THROUGH DAYS 0 – 12*

THIS IS WHERE PEOPLE CAN GET IN TROUBLE

AND/OR

THIS IS WHERE WE CAN INTERVENE



HOW DO WE CHANGE OUTCOME?

WE CHANGE /DECREASE THE DRIVERS

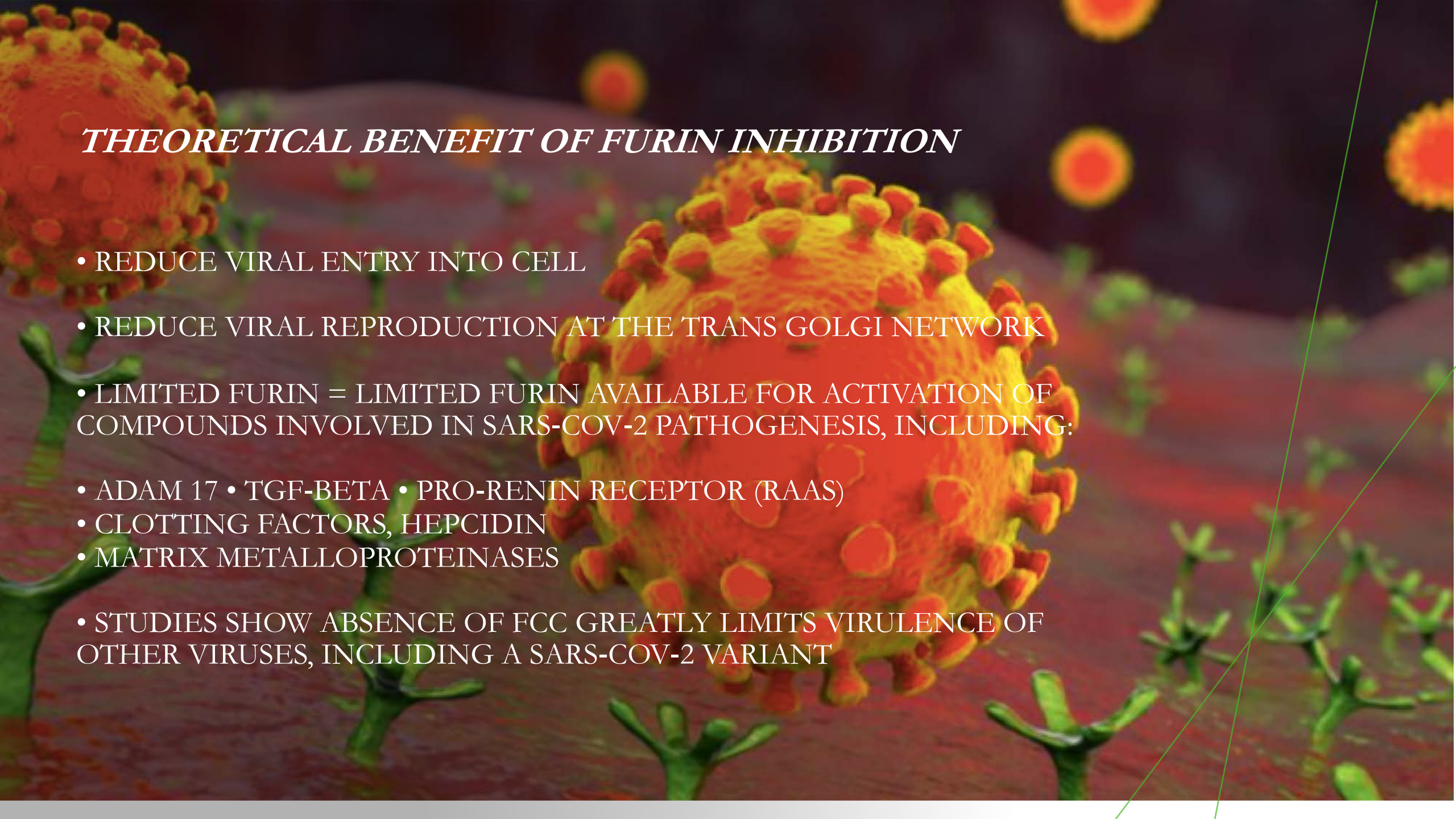
(ANTECEDENTS AND MEDIATORS)

AND WE MODIFY THE

SETTING

ENVIRONMENT

CONTEXT



THEORETICAL BENEFIT OF FURIN INHIBITION

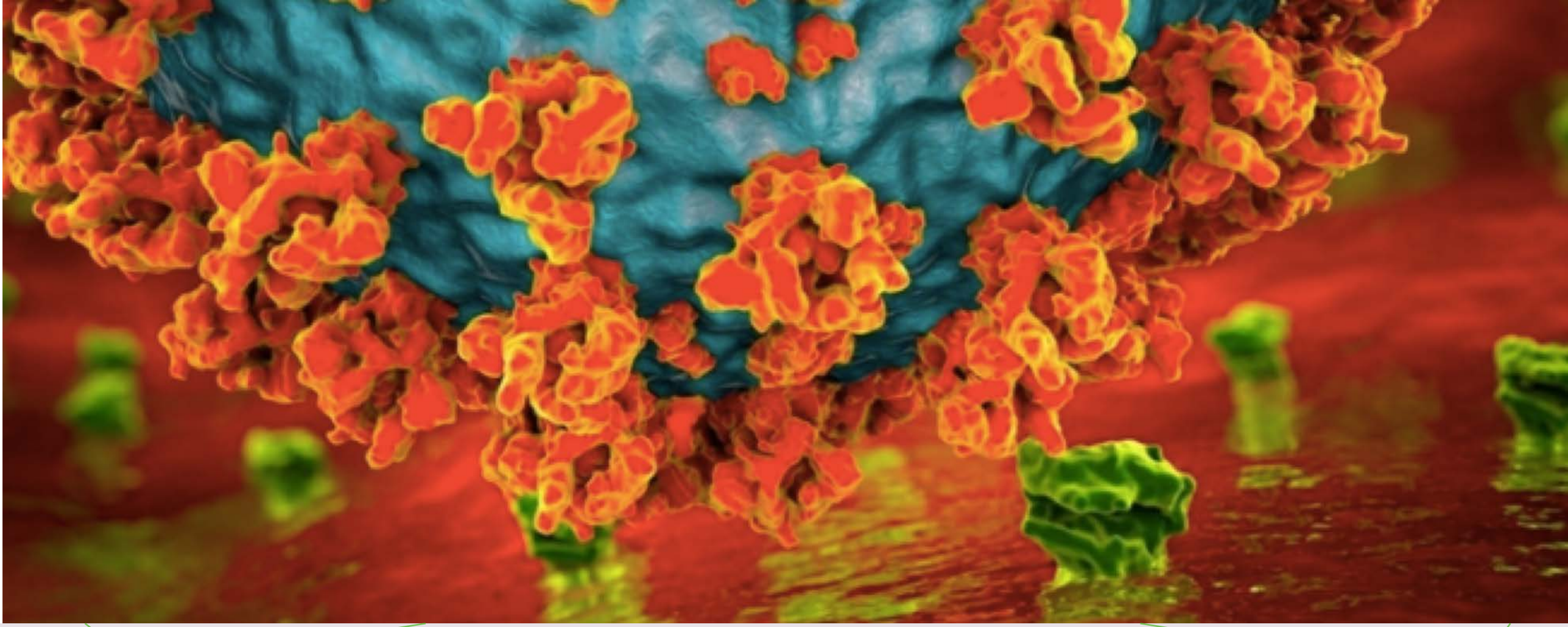
- REDUCE VIRAL ENTRY INTO CELL

- REDUCE VIRAL REPRODUCTION AT THE TRANS GOLGI NETWORK

- LIMITED FURIN = LIMITED FURIN AVAILABLE FOR ACTIVATION OF COMPOUNDS INVOLVED IN SARS-COV-2 PATHOGENESIS, INCLUDING:

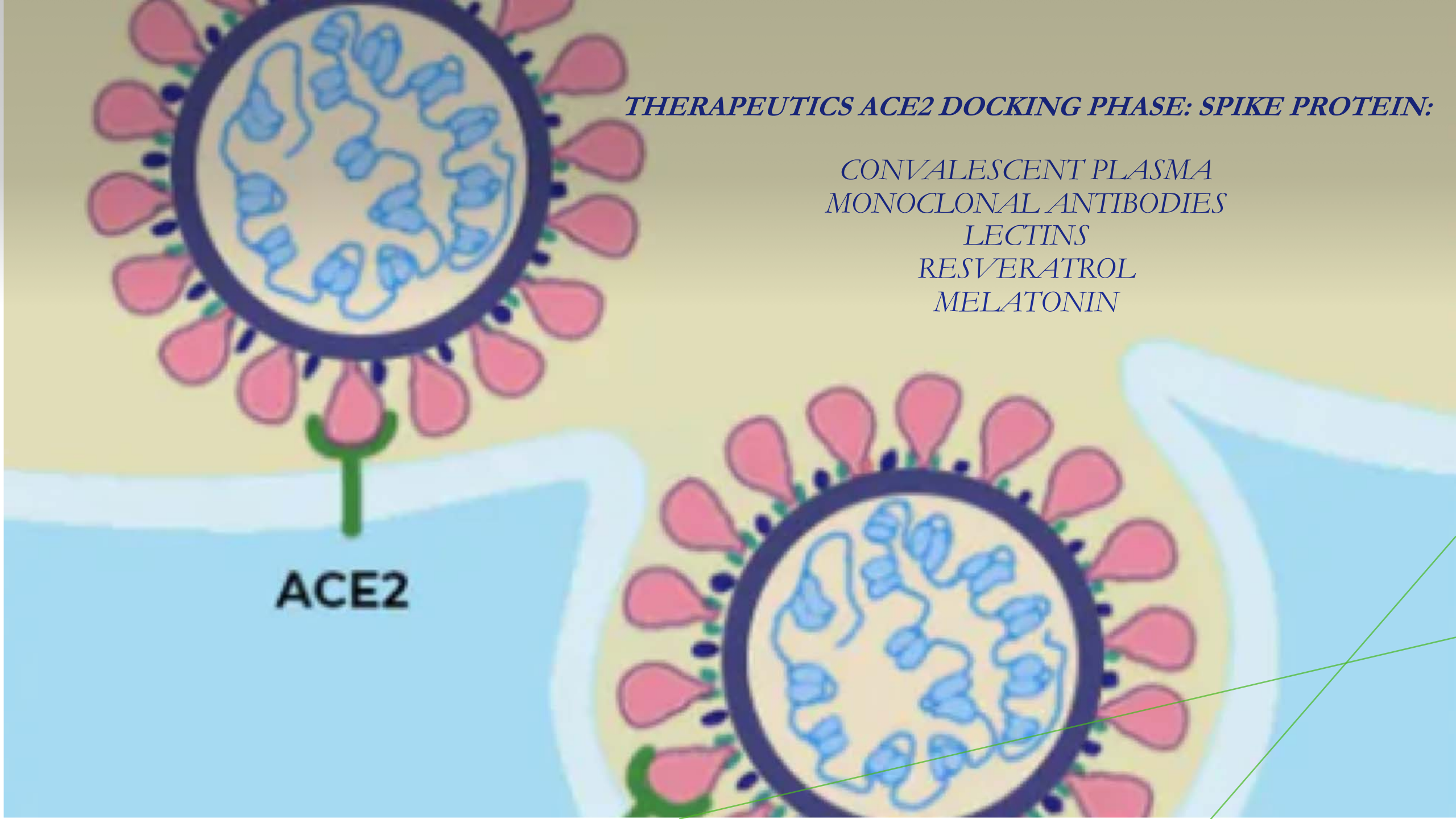
- ADAM 17 • TGF-BETA • PRO-RENIN RECEPTOR (RAAS)
- CLOTTING FACTORS, HEPCIDIN
- MATRIX METALLOPROTEINASES

- STUDIES SHOW ABSENCE OF FCC GREATLY LIMITS VIRULENCE OF OTHER VIRUSES, INCLUDING A SARS-COV-2 VARIANT



SUBSTANCES THAT REDUCE /ACT ON FURIN

ANDROGRAPHICUS
EGCG
GLUTATHIONE
BERBERINE
POSSIBLY HEPARIN POSSIBLY NELFINAVIR



THERAPEUTICS ACE2 DOCKING PHASE: SPIKE PROTEIN:

CONVALESCENT PLASMA
MONOCLONAL ANTIBODIES
LECTINS
RESVERATROL
MELATONIN

TMPRSS2 THERAPEUTICS:

CAMOSTAT

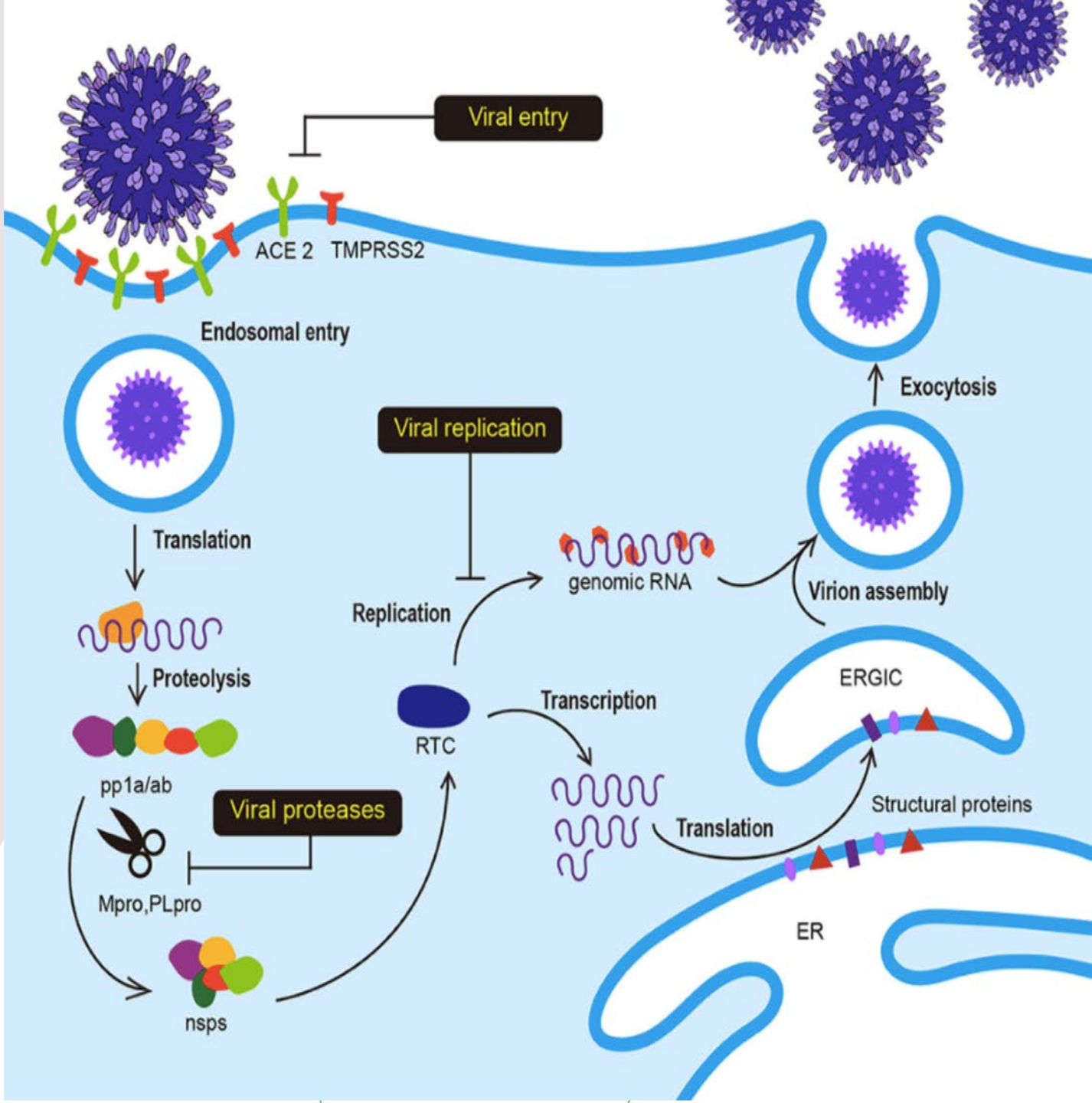
CAMOSTAT MESILATE (CM)
IS AN INHIBITOR OF TMPRSS2

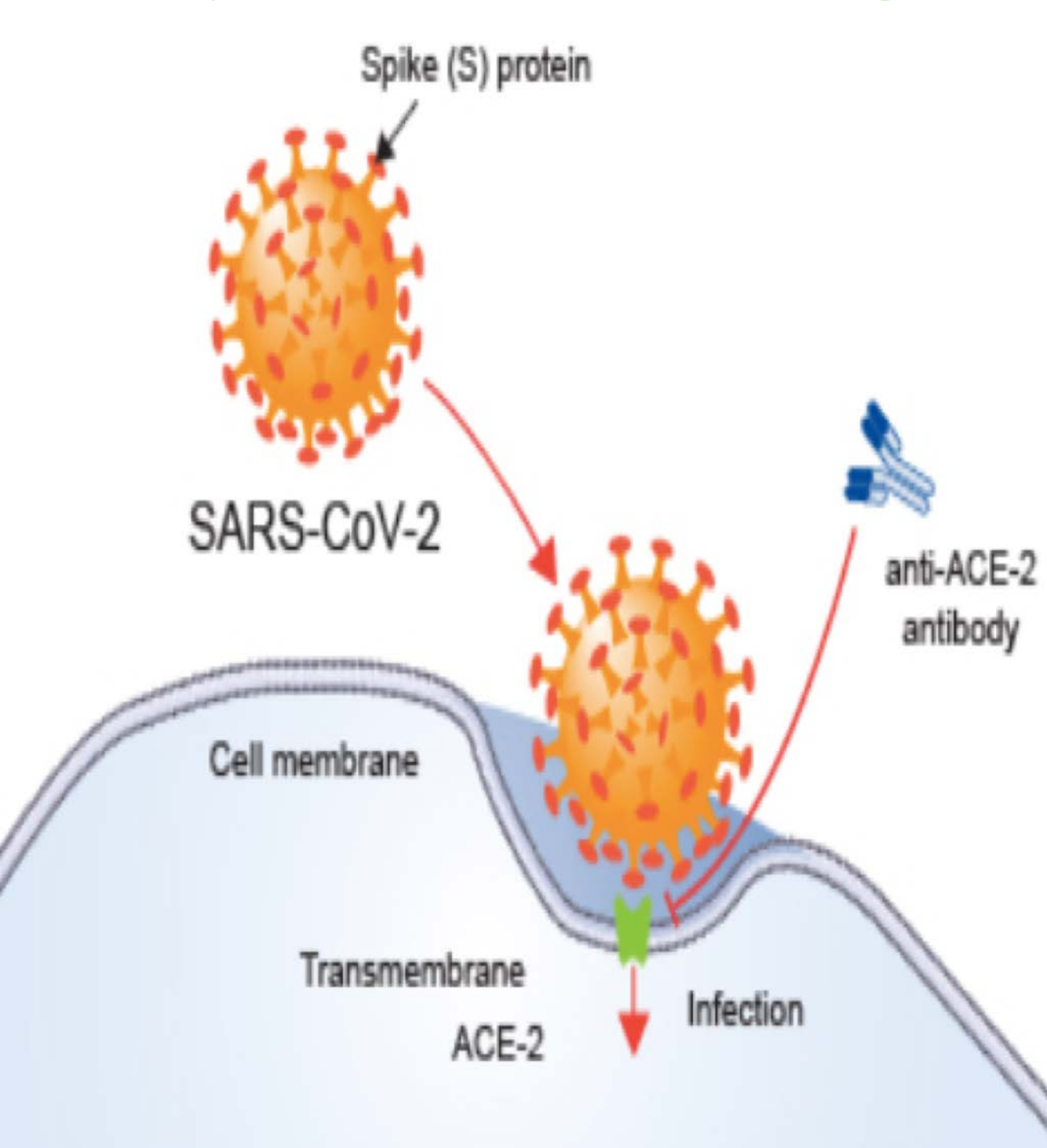
CM BLOCKED THE SPREAD AND PATHOGENESIS OF SARS-COV IN A MOUSE MODEL AND WOULD BE EXPECTED TO SHOW SIMILAR EFFECT IN MERS-COV

(ALSO WORKS AT THE FUSION STEP)

EXPERIMENT SHOWED CM WAS EFFECTIVE IN PROTECTING MICE AGAINST DEATH, FOLLOWING A LETHAL SARS-COV INFECTION, WITH A SURVIVAL RATE OF 60%

HTTPS://WWW.NCBI.NLM.NIH.GOV/PMC/ARTICLES/PMC7188520/





THERAPEUTICS FOCUSED ON VIRAL ENTRY INTO THE CELL

FUSION VS ENDOCYTOSIS

TRANSCRIPTION AND TRANSLATION OF VIRAL RNA

TRANSLATION STEP:
CURCUMIN
QUERCETIN
RESVERATROL

TRANSCRIPTION:
ZINC (ONLY PROPHYLAXIS!)
REMDESIVIR
FAVIPIRAVIR (REPURPOSED INFLUENZA DRUG)
CORONAVIR

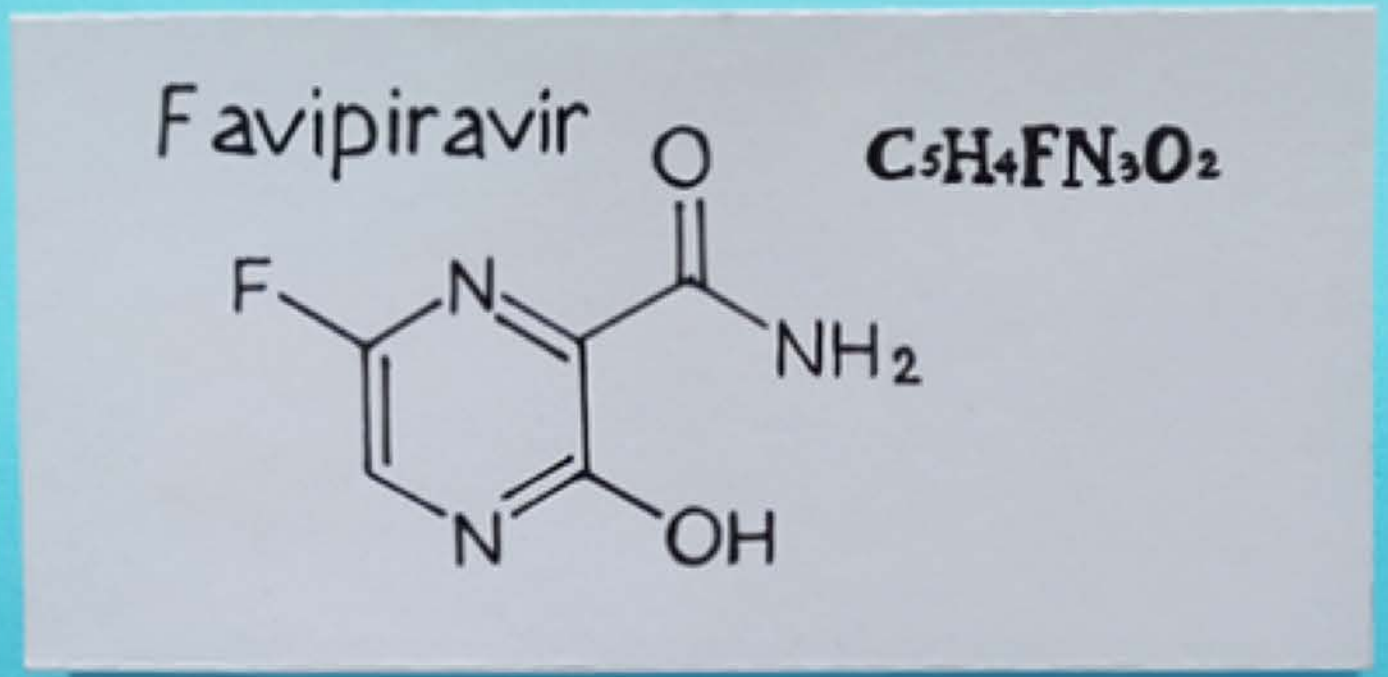
REMDESIVIR

INHIBITS COVID-19 VIRUS POLYMERASE OR REPLICATION MACHINERY. IT WAS RECENTLY FOUND THAT REMDESIVIR STOPS, OR HEAVILY DELAYS REPLICATION OF THE VIRUS, WHICH IN TURN REDUCES PROPAGATION AND SPREAD.

HTTPS://WWW.SCIENCEDAILY.COM/RELEASES/2020/09/200924082656.HTM

FAVIPIRAVIR IS AN ANTIVIRAL DRUG USED FOR INFLUENZA IN JAPAN

IT IS CURRENTLY BEING STUDIED IN HUMANS FOR TREATING COVID-19 IN OVER 30 CLINICAL TRIALS (AS OF JULY 31, 2020). IT IS NOT KNOWN WHETHER IT IS SAFE OR HELPFUL FOR THIS DISEASE.



FAVIPIRAVIR WAS FIRST USED AGAINST SARS-COV-2 IN WUHAN AT THE VERY EPICENTER OF THE PANDEMIC. THEN, AS THE PANDEMIC SPREAD TO EUROPE, THIS DRUG RECEIVED APPROVAL FOR EMERGENCY USE IN ITALY, AND CURRENTLY HAS BEEN IN USE IN JAPAN, RUSSIA, UKRAINE, UZBEKISTAN, MOLDOVA, AND KAZAKHSTAN.
APPROVAL HAS ALSO RECENTLY BEEN GRANTED IN SAUDI ARABIA AND THE UAE. THEREAFTER, TURKEY, BANGLADESH, AND MOST RECENTLY EGYPT HAVE ALSO SEEN RECENT COMMERCIAL LAUNCHES.

HTTPS://WWW.NCBI.NLM.NIH.GOV/PMC/ARTICLES/PMC7467067/

CORONAVIR IS AN INHIBITOR OF SARS-COV-2 RNA POLYMERASE, SIMILAR TO OTHER ANTIVIRAL NUCLEOTIDE ANALOGUES LIKE REMDESIVIR.[1]

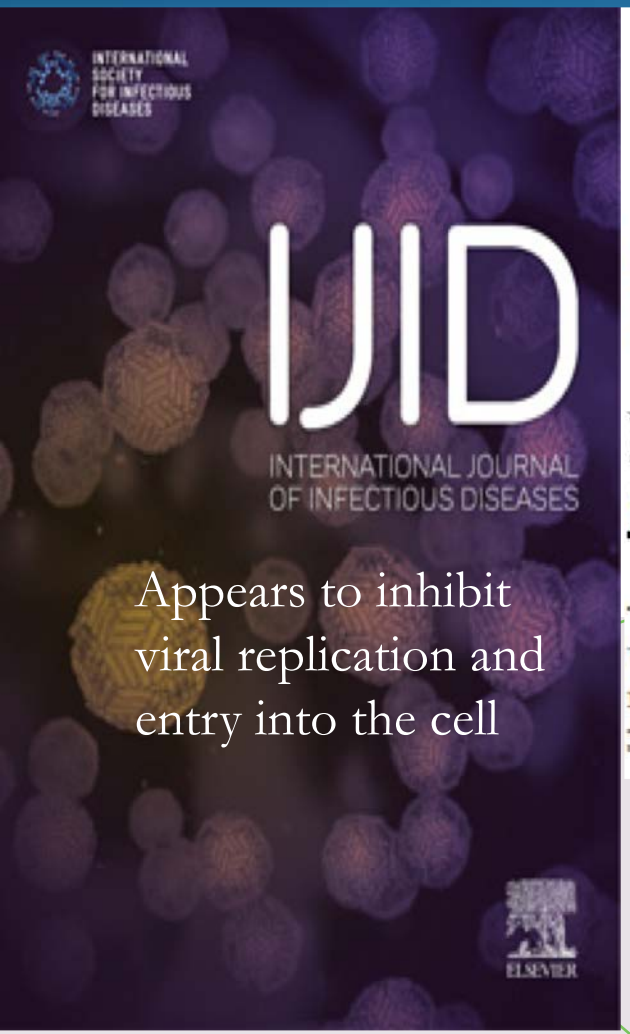
THE DRUG APPEARS TO BE BASED ON FAVIPIRAVIR, A DRUG DEVELOPED IN JAPAN.[3]

CORONAVIR WAS APPROVED FOR USE IN HOSPITALS IN JULY 2020
IN SEPTEMBER 2020 IT RECEIVED APPROVAL FOR PRESCRIPTION SALES FOR OUTPATIENT USE

A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness

Sabeena Ahmed • Mohammad Mahbubul Karim • Allen G. Ross • ... Ahmedul Kabir • Asma Binte Aziz • Wasif Ali Khan • Show all authors

Open Access • Published: December 02, 2020 • DOI: https://doi.org/10.1016/j.ijid.2020.11.191



Appears to inhibit viral replication and entry into the cell

ELSEVIER
International Journal of Antimicrobial Agents
journal homepage: www.elsevier.com/locate/ijantimicag

A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin

Martin D. Hellwig[a,*], Anabela Maia[b]
[a] Plymouth State University, 17 High Street, Plymouth, NH, USA
[b] Rhode Island College, 600 Mount Pleasant Avenue, Providence, RI, USA

ELSEVIER
Antiviral Research
journal homepage: www.elsevier.com/locate/antiviral

The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

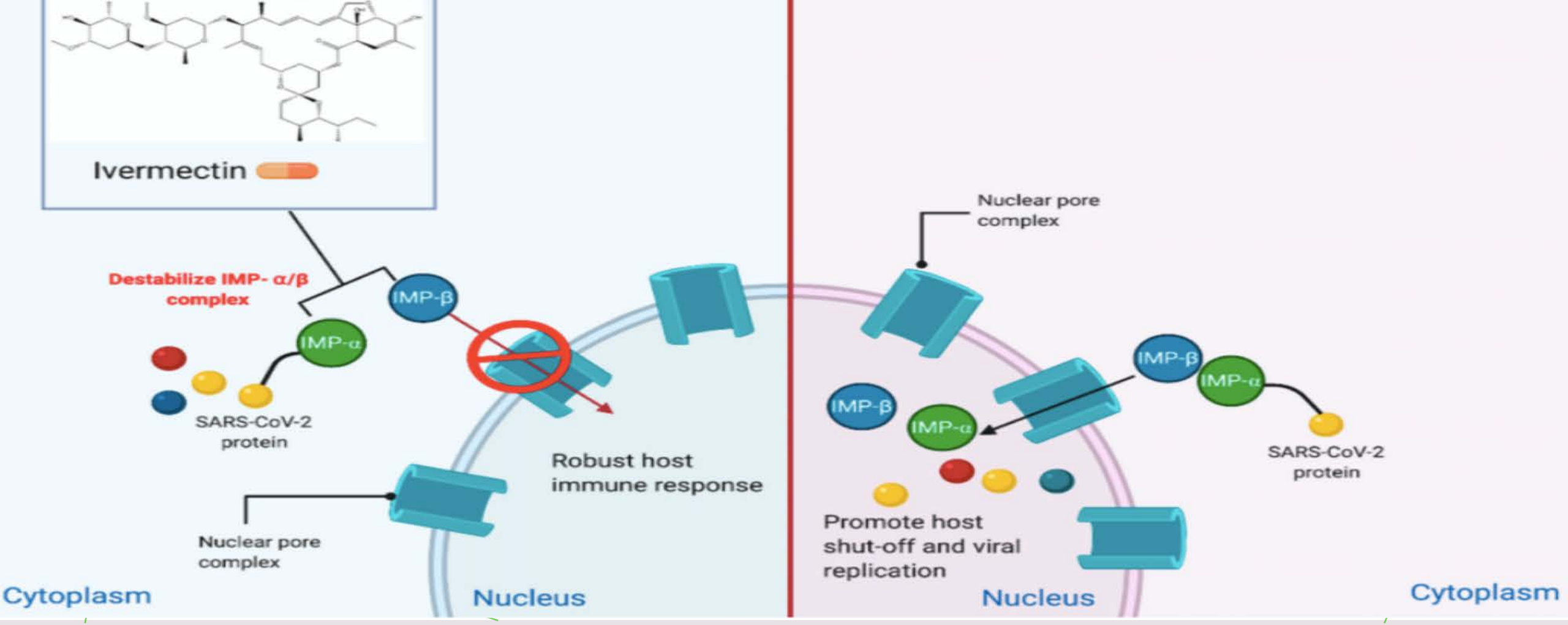
Leon Caly[a], Julian D. Druce[a], Mike G. Catton[a], David A. Jans[b], Kylie M. Wagstaff[b,*]
[a] Victorian Infectious Diseases Reference Laboratory, Royal Melbourne Hospital, At the Peter Doherty Institute for Infection and Immunity, Victoria, 3000, Australia
[b] Biomedicine Discovery Institute, Monash University, Clayton, Vic, 3800, Australia

IVERMECTIN

12 MG INITIALLY, REPEAT IN 3 DAYS

OR

12 MG DAILY X 5 DAYS



DESTABILIZES IMPORTIN a/B COMPLEX

THE APPROVED DOSE OF IVERMECTIN ALONE IS NOT THE IDEAL DOSE FOR THE TREATMENT OF COVID-19

CLIN PHARMACOLOGY AND THERAPEUTICS 2020 OCT;108(4):762-765. DOI: 10.1002/CPT.1889. EPUB 2020 JUN 7.

Caly et al.[1] reported that ivermectin inhibited severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in vitro for up to 48 hours using ivermectin at 5 μM. The concentration resulting in 50% inhibition (IC_{50} ; 2 μM) was > *35× higher than the maximum plasma concentration (C_{max}) after oral administration of the approved dose of ivermectin.*

In summary:

Ivermectin has promise, and a valid mechanism for decreasing viral replication but we may not be able to reach high enough therapeutic levels safely. Combination therapy is more probable, and should be evaluated in vitro

(May be enough though to decrease viral load)

ADDITIONAL POTENTIAL THERAPEUTICS: FLCCC

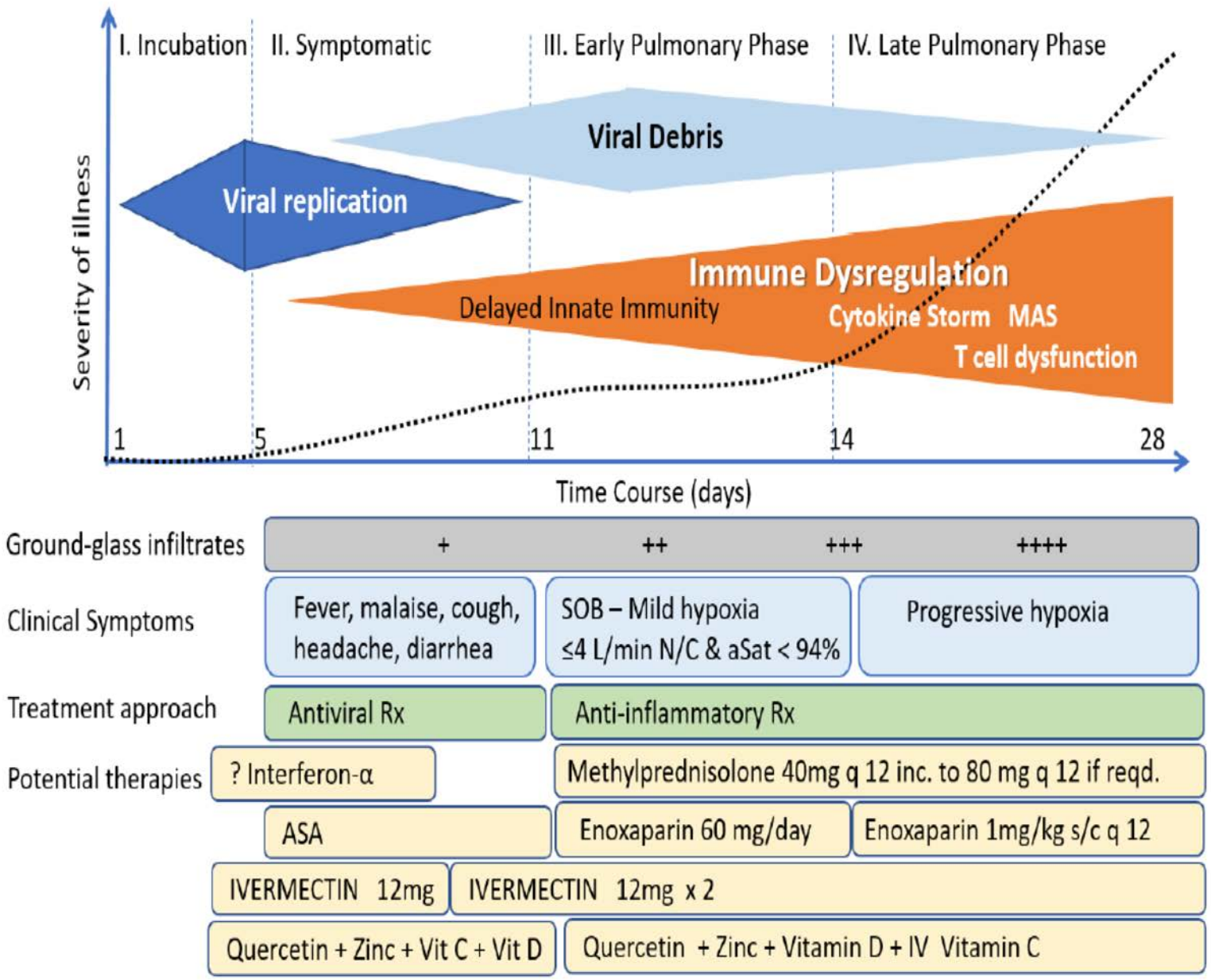
DRUGS UNDER INVESTIGATION

<u>Atorvastatin 80 mg/day.</u>
Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial, and antiviral effects. Statins effect clotting abnormalities by interaction with PAI 1.
Simvastatin has been shown to reduce mortality in the hyper-inflammatory ARDS phenotype. [196]
Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19.[197–201]
(Add CoQ10 & Mg if using Statins)

<u>Famotidine 40 mg BID</u>
20–40 mg/day in renal impairment).
Works on Mast cell/histamine [78–84].

<u>Vascepa, Lovaza or DHA/EPA 4g day</u>
(must also be on antioxidants if using)

Figure 1. The course of COVID-19 and General Approach to treatment



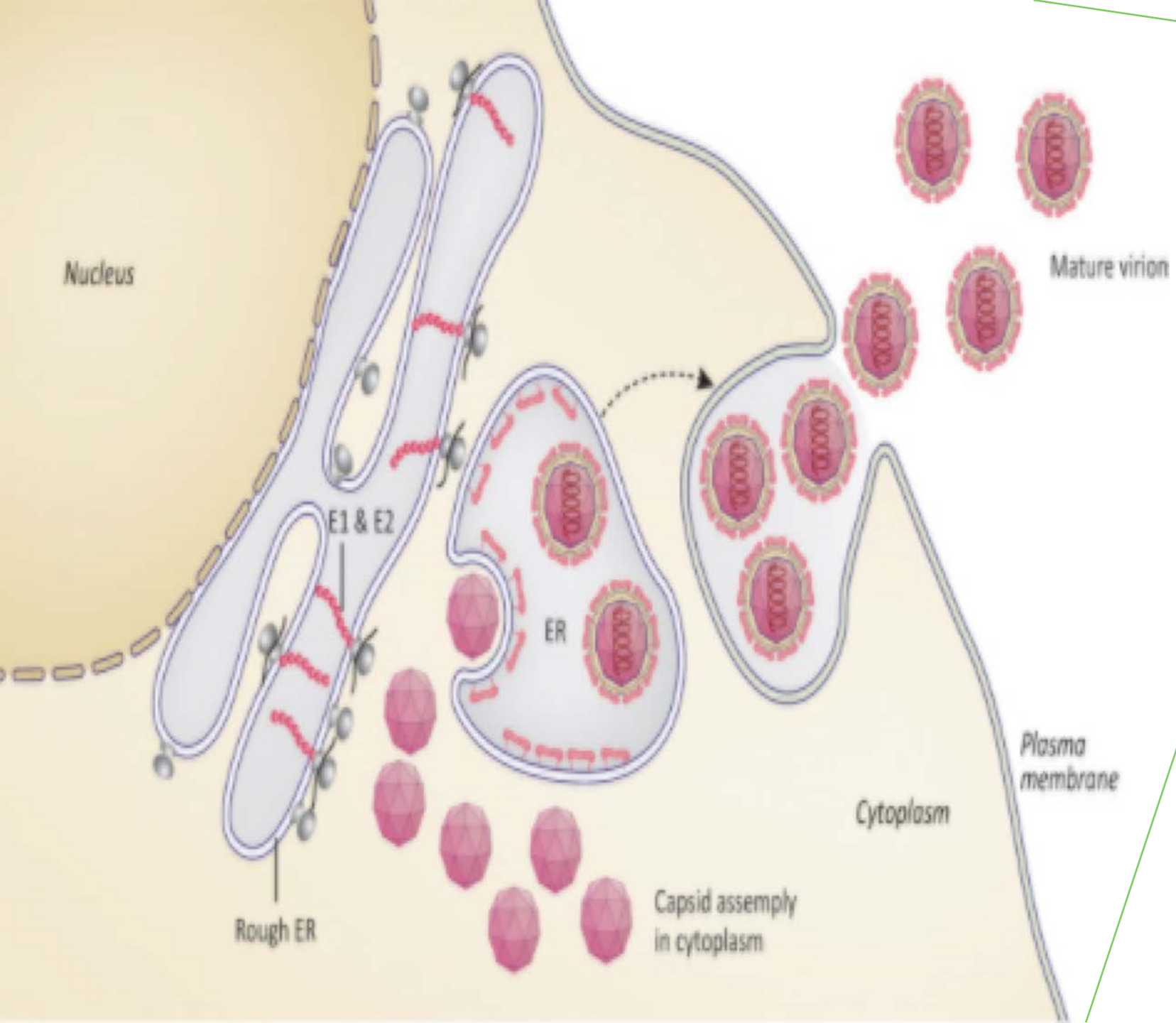
OZONE THERAPY SEEMS TO HAVE AN IMMUNOLOGICAL ROLE BECAUSE OF THE MODULATION OF CYTOKINES AND INTERFERONS, INCLUDING THE INDUCTION OF GAMMA INTERFERON. SYSTEMIC OZONE THERAPY SEEMS TO CONTROL INFLAMMATION, STIMULATE IMMUNITY AND EXHIBITS ANTIVIRAL ACTIVITY . IT PROVIDES PROTECTION FROM ACUTE CORONARY SYNDROMES, ISCHEMIA AND REPERFUSION DAMAGE, THIS SUGGESTS A NEW METHODOLOGY OF IMMUNE THERAPY.

SYSTEMIC OZONE THERAPY IN COMBINATION WITH ANTIVIRALS IN COVID-19-POSITIVE PATIENTS MAY BE JUSTIFIED, HELPFUL AND SYNERGIC.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7585733/#:~:text=Ozone%20exerts%20antiviral%20activity%20through,in%20inflammation%20and%20lung%20damage.

O_3

OZONE



ASSEMBLY
AND
RELEASE OF VIRIONS

CURCUMIN

LECTINS
HTTPS://WWW.NCBI.NLM.NIH.GOV/PMC/ARTICLES/PMC7114093/

NITAZOXANIDE (ALINIA)

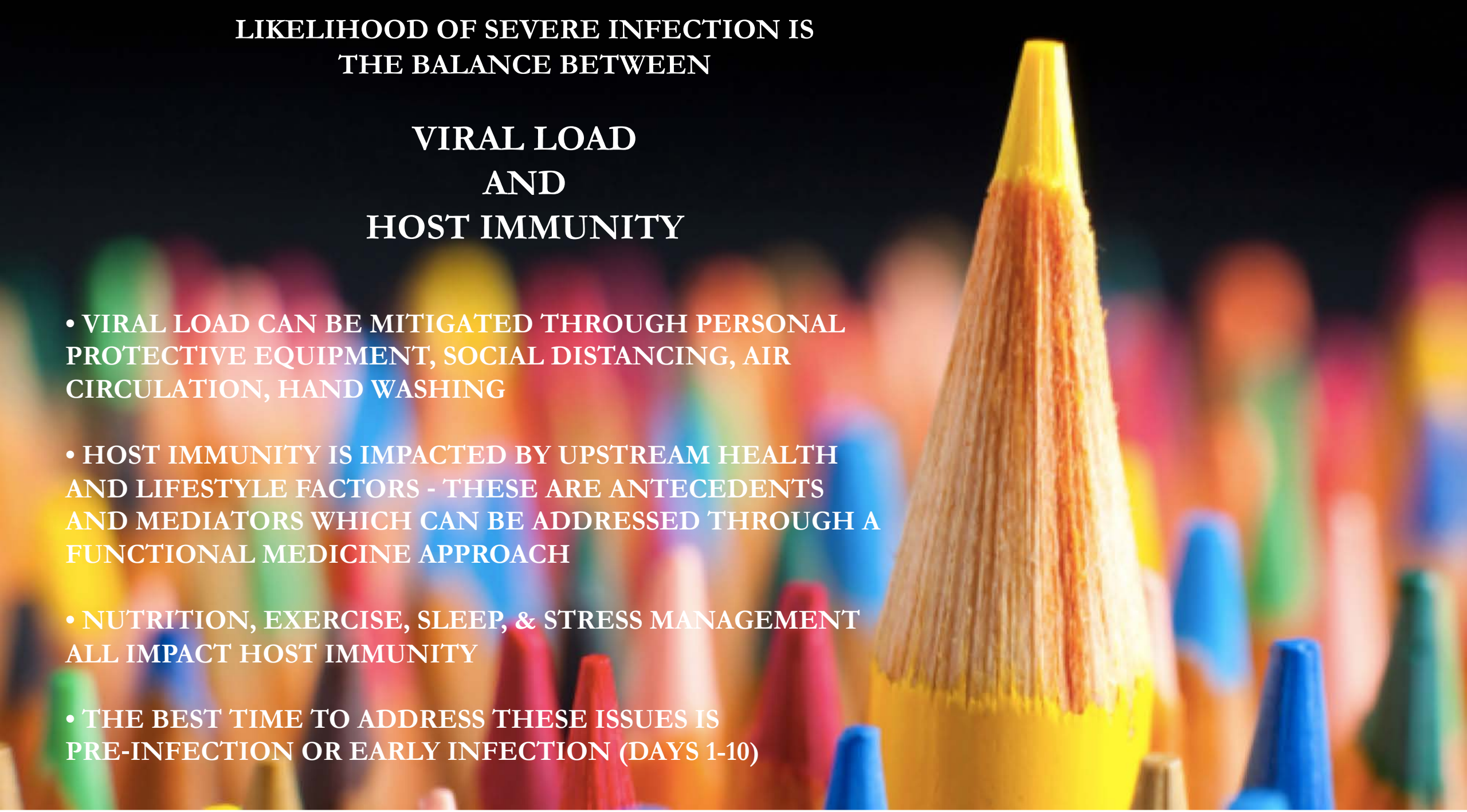
ANTIBODIES

ASSESS AND ADDRESS
EACH PERSON'S UNIQUE VULNERABILITY

1.) LOOK AT GENETICS

2.) ADDRESS:

- *CO-MORBIDITIES*
- *IMMUNE HEALTH*
- *INFLAMMATION*
- *OXIDATIVE STRESS*
- *BIOCHEMICAL IMBALANCES*
- *LIFESTYLE FACTORS*



LIKELIHOOD OF SEVERE INFECTION IS THE BALANCE BETWEEN

VIRAL LOAD AND HOST IMMUNITY

- VIRAL LOAD CAN BE MITIGATED THROUGH PERSONAL PROTECTIVE EQUIPMENT, SOCIAL DISTANCING, AIR CIRCULATION, HAND WASHING

- HOST IMMUNITY IS IMPACTED BY UPSTREAM HEALTH AND LIFESTYLE FACTORS - THESE ARE ANTECEDENTS AND MEDIATORS WHICH CAN BE ADDRESSED THROUGH A FUNCTIONAL MEDICINE APPROACH

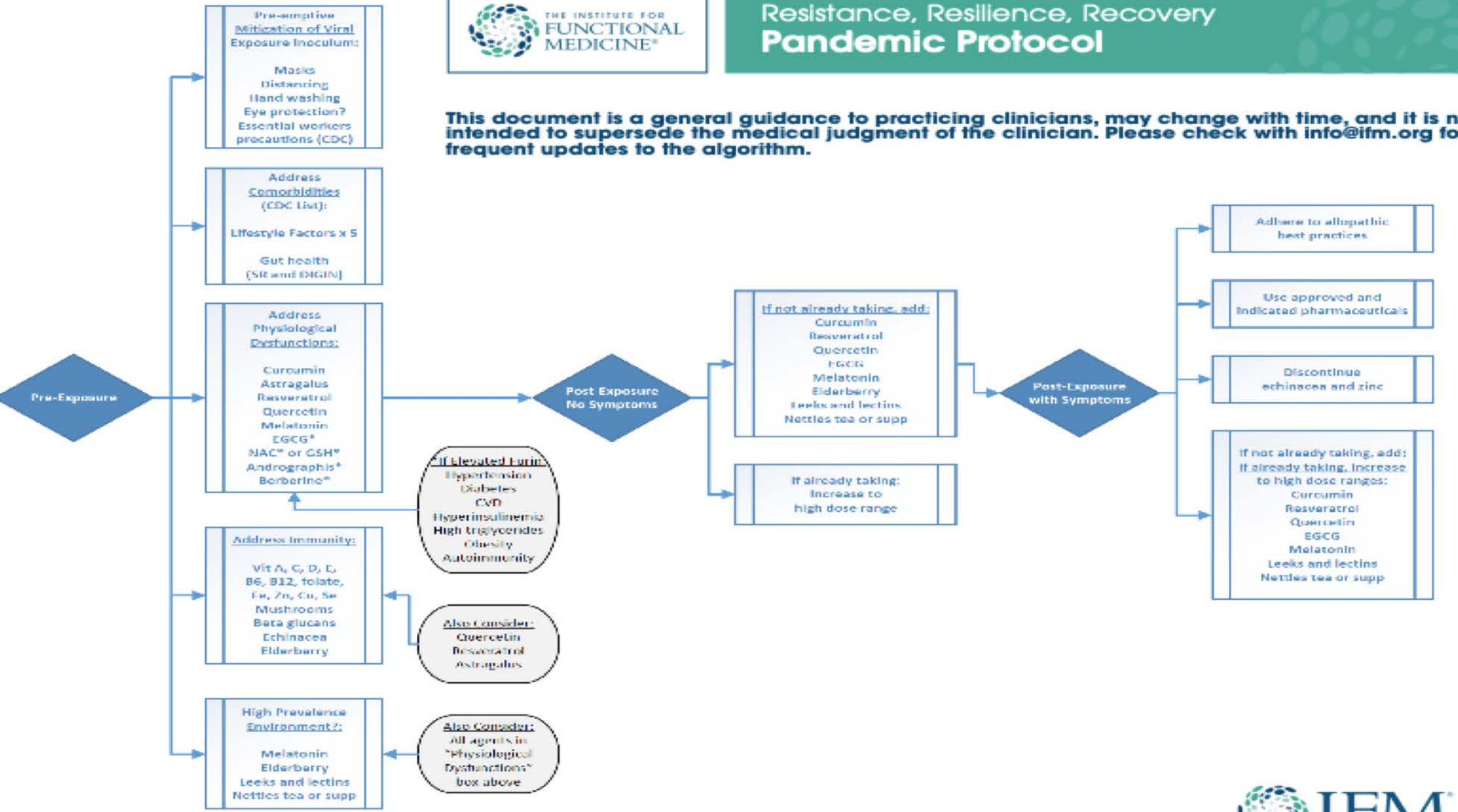
- NUTRITION, EXERCISE, SLEEP, & STRESS MANAGEMENT ALL IMPACT HOST IMMUNITY

- THE BEST TIME TO ADDRESS THESE ISSUES IS PRE-INFECTION OR EARLY INFECTION (DAYS 1-10)

THE INSTITUTE FOR FUNCTIONAL MEDICINE®

Resistance, Resilience, Recovery
Pandemic Protocol

This document is a general guidance to practicing clinicians, may change with time, and it is not intended to supersede the medical judgment of the clinician. Please check with info@ifm.org for frequent updates to the algorithm.



IFM®

Pre-exposure: What to address

Reduce Viral Exposure Load

Mask
Wash Hands
Distancing
Eye protection?
"Essential workers protocol"

Per CDC guidelines
See Unit 3

Comorbidities Obesity

Lifestyle Factors
Sleep
Exercise
Nutrition
Stress
Relationships

See Unit 11

Gut Health

See "Intro to FM"

Individualize

Inflammation Oxidative stress Mitochondropathy Hyperglycemia Furin*

Lifestyle Factors

Gut Health

EGCG*
Curcumin
Astragalus
Quercetin
Resveratrol
NAC* / GSH
Berberine*
Andrographis*

Immune System Resistance Resilience

Mucosal

Consider low dose:
Vit A,C,D,E,B6,B12
Folate, Fe, Zn, Cu, Se

Consider:
Strep. salivarius
LD heparin nasal spr.

Innate

Consider low dose:
Vit A,C,D, NAC, EGCG
Astragulus, Quercetin, Resveratrol,

High Prevalence Environment?

Consider adding:
Melatonin
Elderberry
Leeks & lectins
Nettles (tea/sup)

If not already taking, strongly consider these agents

Post-exposure: Not symptomatic

If not already taking, add:

Melatonin Elderberry	Resveratrol Curcumin	Quercetin EGCG	Leeks Nettles

If already taking, increase to high dose range

Post-exposure: Symptomatic

On admission: Procalcitonin (PCT), CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg.

Discontinue
Zinc
Echinacea

Allopathic best practices

Approved pharma-ceuticals

If not already taking, add;
If already taking, increase to high dose range:

CRP and D-dimer are important prognostic markers. A PCT is essential to rule out coexisting bacterial pneumonia

Resveratrol
Curcumin

Quercetin
EGCG

Leeks
Nettles

Add melatonin: If already taking, increase to 10 – 20 mg qhs

Intervention	Vitamin D
Suggested dose	5,000 IU po qd in the absence of serum levels
Mechanism(s) of action against non-COVID-19 viruses[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76],[77],[78]	Favorably modulate cellular defense and repair mechanisms: •Activation of macrophages •Stimulation of anti-microbial peptides •Modulation of defensins •Modulation of TH17 cells Favorably modulate viral-induced pathological cellular processes: •Reduction in cytokine expression •Modulation of TGF beta
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduce progression from colonization to illness Reduce the severity and duration of acute symptoms and complications
Strength of evidence	Limited
Risk of harm:[79],[80],[81],[82]	Minimal

VITAMIN D

VITAMIN D,1,25(OH) D, IS A STEROID HORMONE AND AN IMMUNE MODULATOR

IT REDUCES INFLAMMATORY CYTOKINES AND INCREASES MACROPHAGE FUNCTION.

VITAMIN D ALSO STIMULATES THE EXPRESSION OF POTENT ANTIMICROBIAL PEPTIDES (AMPS), WHICH EXIST IN NEUTROPHILS, MONOCYTES, NATURAL KILLER CELLS, AND EPITHELIAL CELLS OF THE RESPIRATORY TRACT.[54]

EVIDENCE SUGGESTS VITAMIN D SUPPLEMENTATION MAY PREVENT UPPER RESPIRATORY INFECTIONS.[55]

WE SUGGEST A LABORATORY RANGE OF > 60 AND < 80NG/ML SERUM 25-HYDROXY VITAMIN D MAY HELP TO MITIGATE MORBIDITY FROM COVID-19 INFECTION.

Intervention	Zinc
Suggested dose	30–60 mg daily, in divided doses Zinc acetate, citrate, picolinate, or glycinate orally Zinc gluconate as lozenge
Mechanism(s) of action against non-COVID-19 viruses120,121,122,123,124,125,126,127	Favorably modulate innate and adaptive immune system Favorably modulate viral-induced pathological cellular processes, attachment, and replication
Outcomes data supporting their mitigating effects on illness from other viral strains	Prevention, reduced severity of symptoms, reduced duration of illness, prevention of lower respiratory tract infection
Strength of evidence	Strong
Risk of harm128	Minimal

ZINC

ZINC SUPPORTS BOTH THE INNATE AND THE ADAPTIVE IMMUNE SYSTEM.

EVIDENCE THAT IT SUPPRESSES BOTH VIRAL ATTACHMENT AND REPLICATION.

ZINC DEFICIENCY IS COMMON, ESPECIALLY IN THOSE POPULATIONS MOST AT RISK FOR SEVERE COVID-19 INFECTION. ADDITIONALLY, IT IS NOT ROUTINELY TESTED THEREFORE DEFICIENCY GOES UNDETECTED.

SUPPLEMENTATION WITH ZINC IS SUPPORTED BY ROBUST EVIDENCE. IT PREVENTS VIRAL INFECTIONS AND REDUCES SEVERITY AND DURATION.

REPEATEDLY SHOWN TO REDUCE THE RISK OF LOWER RESPIRATORY INFECTION.

Intervention	Vitamin A
Suggested dose	Up to 10,000-25,000 IU/d
Mechanism(s) of action against non-COVID-19 viruses [95],[96]	Favorably modulate cellular defense and repair mechanisms: • Modulation of T helper cells • Modulation of sIgA Favorably modulate viral-induced pathological cellular processes: • Modulation of cytokine production
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm:[97],[98],[99],[100],[101],[102]	Minimal if does not exceed this dose; caution: pregnancy

VITAMIN A

VITAMIN A IS ANTI-INFLAMMATORY AND ENHANCES IMMUNE FUNCTION.

VITAMIN A IS INVOLVED IN THE DEVELOPMENT OF THE IMMUNE SYSTEM AND PLAYS REGULATORY ROLES IN CELLULAR IMMUNE RESPONSES AND HUMORAL IMMUNE PROCESSES VIA THE MODULATION OF T HELPER CELLS, sIgA, AND CYTOKINE PRODUCTION.

VITAMIN A IS CRUCIAL FOR MAINTAINING VISION, PROMOTING GROWTH AND DEVELOPMENT, AND PROTECTING EPITHELIUM AND MUCOSAL INTEGRITY.

Intervention	**Melatonin**
Suggested dose	5-20 mg qd
Mechanism(s) of action against non-COVID-19 viruses [83],[84]	Favorably modulate viral-induced pathological cellular processes • Modulation of NLRP3 inflammasome activation [83],[84]
Outcomes data supporting their mitigating effects on illness from other viral strains	Research in progress
Strength of evidence	Conditional
Risk of harm: [86],[87],[88],[89],[90],[91],[92],[93],[94]	Minimal

MELATONIN

MELATONIN HAS BEEN SHOWN TO HAVE AN INHIBITORY EFFECT ON THE NLRP3 INFLAMMASOME.[94]

THIS HAS NOT GONE UNNOTICED BY THE COVID-19 RESEARCH COMMUNITY, WITH TWO RECENT PUBLISHED PAPERS PROPOSING THE USE OF MELATONIN AS A THERAPEUTIC AGENT IN THE TREATMENT OF PATIENTS WITH COVID-19.[84],[85]

Intervention	Quercetin
Suggested dose	Regular: 1 gm po bid; phytosome 500 mg bid
Mechanism(s) of action against non-COVID-19 viruses	Promote viral eradication or inactivation:[9],[10],[11],[12],[13] •Inhibition of viral replication Favorably modulate viral-induced pathological cellular processes: •Modulation of NLRP3 inflammasome activation[5],[14],[15] Mechanistically promote resolution of collateral damage and restoration of function: •Modulation of mast cell stabilization (anti-fibrotic)
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduction of symptoms
Strength of evidence	Moderate
Risk of harm:[16],[17]	Minimal

QUERCETIN

QUERCETIN HAS BEEN SHOWN TO HAVE ANTIVIRAL EFFECTS

AGAINST BOTH RNA (E.G., INFLUENZA AND CORONAVIRUS) AND DNA VIRUSES (E.G., HERPESVIRUS).

QUERCETIN HAS A PLEIOTROPIC ROLE AS AN ANTIOXIDANT AND ANTI-INFLAMMATORY, IT MODULATES SIGNALING PATHWAYS THAT ARE ASSOCIATED WITH POST-TRANSCRIPTIONAL MODULATORS AND IT AFFECTS POST-VIRAL HEALING.[8]

Intervention	N-acetylcysteine (NAC)
Suggested dose	600-900 mg po bid
Mechanism(s) of action against non-COVID-19 viruses:[36]	Favorably modulate cellular defense and repair mechanisms: •Hypothetical: repletion of glutathione and cysteine
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduce progression from colonization to illness Reduce the severity and duration of acute symptoms
Strength of evidence	Limited
Risk of harm:[37],[38],[39],[40],[41]	Minimal

N-ACETYLCYSTEINE (NAC) (GLUTATHIONE)

N-ACETYLCYSTEINE PROMOTES GLUTATHIONE PRODUCTION, WHICH HAS BEEN SHOWN TO BE PROTECTIVE IN THOSE INFECTED WITH INFLUENZA AND OTHER VIRUSES.

GLUTATHIONE IS A POTENT ANTIOXIDANT AND IS HELPFUL WITH CELLULAR REPAIR

IN A SIX-MONTH CONTROLLED STUDY ENROLLING PRIMARILY ELDERLY SUBJECTS, THOSE RECEIVING 600 MG NAC TWICE DAILY, AS OPPOSED TO PLACEBO, EXPERIENCED SIGNIFICANTLY FEWER INFLUENZA-LIKE SYMPTOMS AND DAYS OF BED CONFINEMENT.[36]

Intervention	Curcumin
Suggested dose	500-1,000 mg po bid (of absorption-enhanced curcumin)
Mechanism(s) of action against non-COVID-19 viruses	Favorably modulate viral-induced pathological cellular processes: •Modulation of NLRP3 inflammasome activation[5],[19],[20],[21]
Outcomes data supporting their mitigating effects on illness from other viral strains No data available	No data available
Strength of evidence	Conditional
Risk of harm:[22],[23],[24],[25],[26],[27]	Minimal

CURCUMIN

CURCUMIN HAS BEEN SHOWN TO MODULATE THE NLRP3 INFLAMMASOME,(5) AND A PREPRINT SUGGESTS THAT CURCUMIN CAN REDUCE VIRAL REPLICATION BY TARGETING THE SARS-COV-2 MAIN PROTEASE.(18)

Intervention	Resveratrol
Suggested dose	100-150 mg po qd
Mechanism(s) of action against non-COVID-19 viruses	Favorably modulate viral-induced pathological cellular processes •Modulation of NLRP3 inflammasome activation[5]
Outcomes data supporting their mitigating effects on illness from other viral strains	MERS-CoV[43] Influenza[44],[45]
Strength of evidence	Conditional
Risk of harm:[46],[47],[48],[49],[50],[51],[52],[53]	Minimal

RESVERATROL

RESVERATROL SHOWS MANY BENEFICIAL HEALTH EFFECTS.

IT HAS BEEN SHOWN TO MODULATE THE NLRP3 INFLAMMASOME.[5]

RESVERATROL WAS SHOWN TO HAVE IN VITRO ACTIVITY AGAINST MERS-COV.[43]

Intervention	Vitamin C
Suggested dose	1-3 grams po qd
Mechanism(s) of action against non-COVID-19 viruses [12]	Favorably modulate cellular defense and repair mechanisms Favorably modulate viral-induced pathological cellular processes
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Strong
Risk of harm[121]	Minimal

VITAMIN C

VITAMIN C CONTRIBUTES TO IMMUNE DEFENSE BY SUPPORTING CELLULAR FUNCTIONS OF BOTH THE INNATE AND ADAPTIVE IMMUNE SYSTEM.

VITAMIN C ACCUMULATES IN PHAGOCYTIC CELLS, SUCH AS NEUTROPHILS, AND CAN ENHANCE CHEMOTAXIS, PHAGOCYTOSIS, GENERATION OF REACTIVE OXYGEN SPECIES, AND ULTIMATELY MICROBIAL KILLING.

SUPPLEMENTATION WITH VITAMIN C APPEARS TO BOTH PREVENT AND TREAT RESPIRATORY AND SYSTEMIC INFECTIONS.[120]

VITAMIN C HAS BEEN USED IN HOSPITAL ICUS TO TREAT COVID-19 INFECTION.

Intervention	Berberine
Suggested dose	500 mg, 2-3 times daily
Mechanism(s) of action against non-COVID-19 viruses	Priming innate immune function[125,126,127] Aldose reductase inhibition[128] Promoting viral eradication or inactivation[117,118,119,129,130,131,132]
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Limited
Risk of harm	Minimal[133,134,135,136,137]

BERBERINE

BERBERINE HAS BEEN SHOWN TO HAVE ANTI-VIRAL ACTIVITY ACROSS A BROAD RANGE OF VIRAL TARGETS.115,116,117,118,119,120 BERBERINE ALSO ACTIVATES 5' AMP-ACTIVATED PROTEIN KINASE (AMPK),121,122 WHICH IS DIRECTLY ANTI-INFLAMMATORY. BERBERINE'S ANTI-INFLAMMATORY EFFECTS ALSO INCLUDE SUPPRESSION OF INHIBITION OF IKB KINASE AND DOWNREGULATION OF NFKB, IL-1?, AND TNF?.123

BERBERINE ALSO ACTS TO LOWER BLOOD GLUCOSE,124 THUS HELPING WITH FURIN INHIBITION, AS WELL AS PRESERVING ACE2 RECEPTORS, POSSIBLY THROUGH ALDOSE REDUCTASE INHIBITION.

Intervention	Elderberry
Suggested Dose	500 mg po QD (of USP standard of 17% anthocyanosides)
Mechanism(s) of action against non-COVID-19 viruses[103],[107],[108],[109],[110],[111],[112]	Favorably modulate cellular defense and repair mechanisms Favorably modulate viral-induced pathological cellular processes
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Strong
Risk of harm:[103],[107],[113],[114]	Minimal; caution with autoimmune disease; uncooked/unripe plant parts toxic; USDA GRAS

ELDERBERRY

ELDERBERRY (SAMBUCUS NIGRA) HAS WIDESPREAD HISTORICAL USE AS A SAFE ANTI-VIRAL HERB.[103]

ELDERBERRY IS MOST EFFECTIVE IN THE PREVENTION OF INFECTION AND DURING THE EARLY PHASES OF INFECTION WITH RESPIRATORY VIRUSES.[104]

Intervention	Licorice (Glycyrrhiza glabra)
Suggested dose	Licorice root standardized to glycyrrhizin. 200-400 mg daily in divided doses. Short term use: <4 weeks.
Mechanism(s) of action against non-COVID-19 viruses	Promoting viral eradication or inactivation[29,54,55,56,62,65,66] Favorably modulating inflammation
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduction of symptoms[69,70]
Strength of evidence	Moderate
Risk of harm[71, 72, 73, 74]	Minimal, if short-term use (< 4 weeks) [69,70,71,72]

LICORICE (GLYCYRRHIZA SPECIES)

LICORICE MECHANISMS OF ACTION, INCLUDE, INHIBITION OF VIRAL REPLICATION55,56,57 BLOCKING THE ACE2 RECEPTOR,58 PROMOTING THE ACTIVITY OF TH1 CELLS,59 AND INHIBITION OF PRO-INFLAMMATORY CYTOKINES,60 PROSTAGLANDINS, AND NITRIC OXIDE PRODUCTION.61 THE INHIBITION OF HYDROCORTISONE METABOLISM HAS ALSO BEEN SUGGESTED AS A POTENTIAL MECHANISM OF LICORICE'S ANTI-INFLAMMATORY ACTION.62 LICORICE HAS BEEN USED AGAINST SARS-COV-1 AND H1N1 AND REVIEWED FOR ITS EFFECTS ON SARS-COV-2.63,64 TWO POSITIVE HUMAN TRIALS HAVE BEEN PERFORMED AGAINST SARS-COV-1 USING LICORICE.65,66

Intervention	Andrographis (Andrographis paniculata)
Suggested dose	Standardized extract (typically 30% andrographolides) 100-600 mg daily, most often delivered in combination with other herbal preparations.
Mechanism(s) of action against non-COVID-19 viruses	Inhibition of furin protease[86] Priming innate immune function[81] Promoting viral eradication or inactivation[74]
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduction of symptoms[76,87,88,89]
Strength of evidence	Strong
Risk of harm	Minimal[90,91,92]

ANDROGRAPHIS PANICULATA

ANDROGRAPHIS ACTS TO DECREASE THE ACTIVITY OF FURIN PROTEASE, A NECESSARY STEP IN SARS-COV-2 SPIKE PROTEIN ACTIVATION WHICH ALLOWS FOR VIRAL INSERTION INTO MUCOSAL EPITHELIAL CELLS.86

ANDROGRAPHIS HAS DEMONSTRATED ANTI-INFLAMMATORY, ANTIVIRAL, AND IMMUNE-STIMULATORY ACTIVITIES AND HAS BEEN SHOWN, IN VITRO, TO BE EFFECTIVE AGAINST AVIAN INFLUENZA A (H9N2 AND H5N1) AND HUMAN INFLUENZA A H1N1 VIRUSES.77,78

SHOWN TO INHIBIT PLATELET-ACTIVATING FACTOR–MEDIATED INFLAMMATORY RESPONSES, AND TO REDUCE THE EXPRESSION OF CYCLOOXYGENASE-2

IT HAS ANALGESIC AS WELL AS ANTIPYRETIC EFFECTS.79,80,81,82,83,84,85

Intervention	Epigallocatechin gallate (EGCG)
Suggested dose	4 cups daily or 225 mg po QD
Mechanism(s) of action against non-COVID-19 viruses	Favorably modulate viral-induced pathological cellular processes: •Modulation of NLRP3 inflammasome activation[5],[28],[29]
Outcomes data supporting their mitigating effects on illness from other viral strains	No data available
Strength of evidence	Conditional
Risk of harm:[30],[31],[32],[33],[34],[35]	Significant (rare) - Hepatotoxicity

EPIGALLOCATECHIN GALLATE (EGCG)

GREEN TEA

GREEN TEA MODULATES THE NLRP3 INFLAMMASOME AND TARGETS THE SARS-COV-2 MAIN PROTEASE (MPRO)7 TO REDUCE VIRAL REPLICATION

EGCG HAS ALSO BEEN SHOWN TO PREVENT INFLUENZA IN HEALTHCARE WORKERS (28)

Intervention	Luteolin
Suggested dose	100-200 mg, 2-3 times daily
Mechanism(s) of action against non-COVID-19 viruses	Mpro inhibition[165,166] Inhibition of wild-type SARS-CoV infection[167] Binding to viral S protein and furin inhibition[168] Promoting viral eradication or inactivation[169,170,171] Modulation of inflammation [172]
Outcomes data supporting their mitigating effects on illness from other viral strains	Inconclusive
Strength of evidence	Conditional

LUTEOLIN

LUTEOLIN IS A FLAVONOID FOUND IN PEPPERS, CELERY, RADICCHIO, CHICORY, AND LEMONS. PLANTS RICH IN LUTEOLIN HAVE BEEN USED IN THE TREATMENT OF HYPERTENSION, INFLAMMATORY DISORDERS, AND CANCER.164 RECENT SCREENING STUDIES HAVE IDENTIFIED LUTEOLIN AS A CANDIDATE MOLECULE TO BLOCK SARS-COV-2 ENTRY INTO THE CELL AS WELL AS TO MODULATE EXCESSIVE INFLAMMATORY RESPONSES.

Intervention	Echinacea species (E. purpurea, E. angustifolia, and E. pallida)
Suggested dose	Varied. Given the variety of active ingredients in various species and the variability of the extraction processes, it is suggested that dosing instructions be individualized based on research of specific Echinacea species.
Mechanism(s) of action against non-COVID-19 viruses	Priming innate immune function[139,140,141,142,143,144,145] Promoting viral eradication or inactivation[146,147,148]
Outcomes data supporting their mitigating effects on illness from other viral strains	Prevention of infection[156,157,158] Reduced duration of symptoms[159,160]
Strength of evidence	Strong (for prevention) Conditional (for treatment—conflicting studies)

ECHINACEA

ECHINACEA PURPUREA HAS BEEN SHOWN TO STIMULATE MACROPHAGE ACTIVATION AS WELL AS NK CELL ACTIVITY IN BOTH HUMAN AND ANIMAL MODELS AND MAY BE LINKED DIRECTLY TO INCREASED CYTOKINE EXPRESSION.144,145VARIOUS ECHINACEA HAS SHOWN ANTIVIRAL ACTIVITY.146,147,148

ECHINACEA ALONE HAS BEEN SHOWN TO REDUCE THE FREQUENCY, SEVERITY, AND/OR DURATION OF UPPER RESPIRATORY TRACT SYMPTOMS IN SEVERAL TRIALS

Intervention	Chinese skullcap (Scutellaria baicalensis)
Suggested dose	750–1,500 mg daily standardized to flavonoids, baicalin, or baicalein. Given the variability of standardization, it is suggested that dosing instructions should be based on research of specific standardized extracts.
Mechanism(s) of action against non-COVID-19 viruses	Priming innate immune function[36,41,42] Promoting viral eradication or inactivation[36-41] Favorably modulating pulmonary inflammation[38,41,43,44,45,46,47,48]
Outcomes data supporting their mitigating effects on illness from other viral strains	Reduction of symptoms[49]
Strength of evidence	Limited
Risk of harm	Minimal, though combination product showed significant hepatotoxicity.[50,51,52,53,54]

CHINESE SKULLCAP (SCUTELLARIA BAICALENSIS)

IN TRIALS, PARTICIPANTS WHO TOOK CHINESE SKULLCAP SHOWED STATISTICALLY SIGNIFICANT DECREASES IN VIRAL INFECTION RATES COMPARED TO CONTROLS.30

CHINESE SKULLCAP HAS ANTI-INFLAMMATORY, ANTIOXIDANT, ANTIBACTERIAL, AND ANTIVIRAL EFFECTS.31,32,33
IT HAS BEEN SHOWN TO INCREASE IMMUNE SURVEILLANCE AND DOWNREGULATE NLRP3 INFLAMMASOMES,34 IL-6, AND TNF-ALPHA.35

The Functional Medicine Model

The Functional Medicine model is an individualized, patient-centered, science-based approach that identifies and addresses the underlying causes of disease and promotes optimal wellness.

It utilizes a detailed understanding of each patient's genetic, biochemical, and lifestyle factors and leverages that data to direct personalized treatment plans that lead to improved patient outcomes.

The Institute for Functional Medicine. 2020. *Functional Medicine | IFM*. [online] Available at: <https://www.ifm.org/functional-medicine/> [Accessed 18 September 2020]

REAL CHANGES YOU CAN MAKE NOW TO *CONTROL YOUR COVID OUTCOME*

PERSONALIZED COVID TREATMENT PLANS DEVELOPED FROM LATEST SCIENCE

FUNCTIONAL
MEDICINE SPECIALISTS

Cambria DeMarco, ACNP-BC, MSN, BA, BSN
IFM Practitioner
Walsh & Bredesen Protocol Certified
www.fmscal.com

760.270.3990

FUNCTIONAL

MEDICINE SPECIALISTS

CAMBRIA DEMARCO, ACNP-BC, MSN, BSN, BA

IFM PRACTITIONER

WALSH & BREDESEN PROTOCOL CERTIFIED PRACTITIONER

WWW.FMSCAL.COM

317 N EL CAMINO REAL, SUITE #407

ENCINITAS, CA 92024

760-270-3990