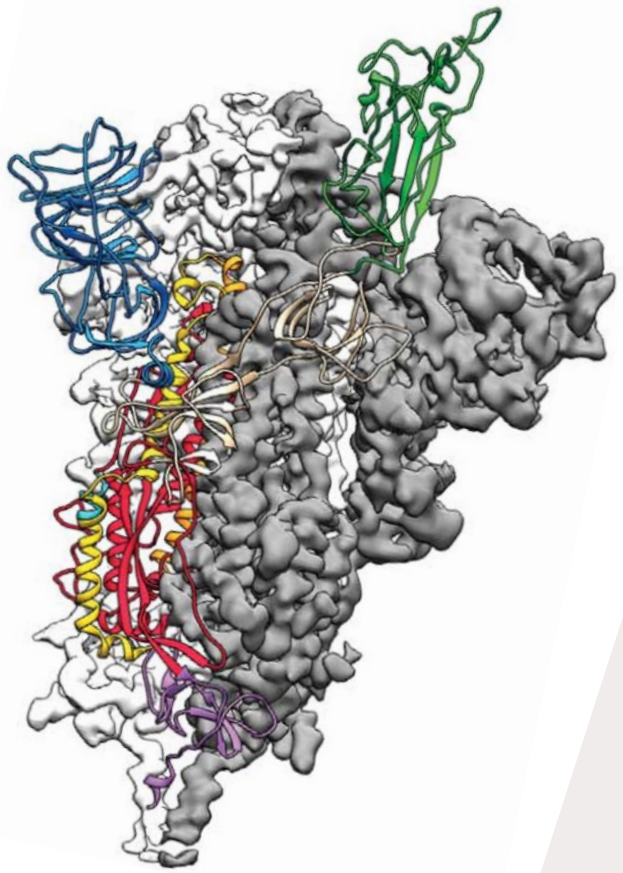


DAVID C. SOCOL, MD

AUGUST 16, 2023

2023 COVID Update: Through the Lens of Functional Medicine

Daniel, W., & Wang, N. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 10.1126/science.abb2507

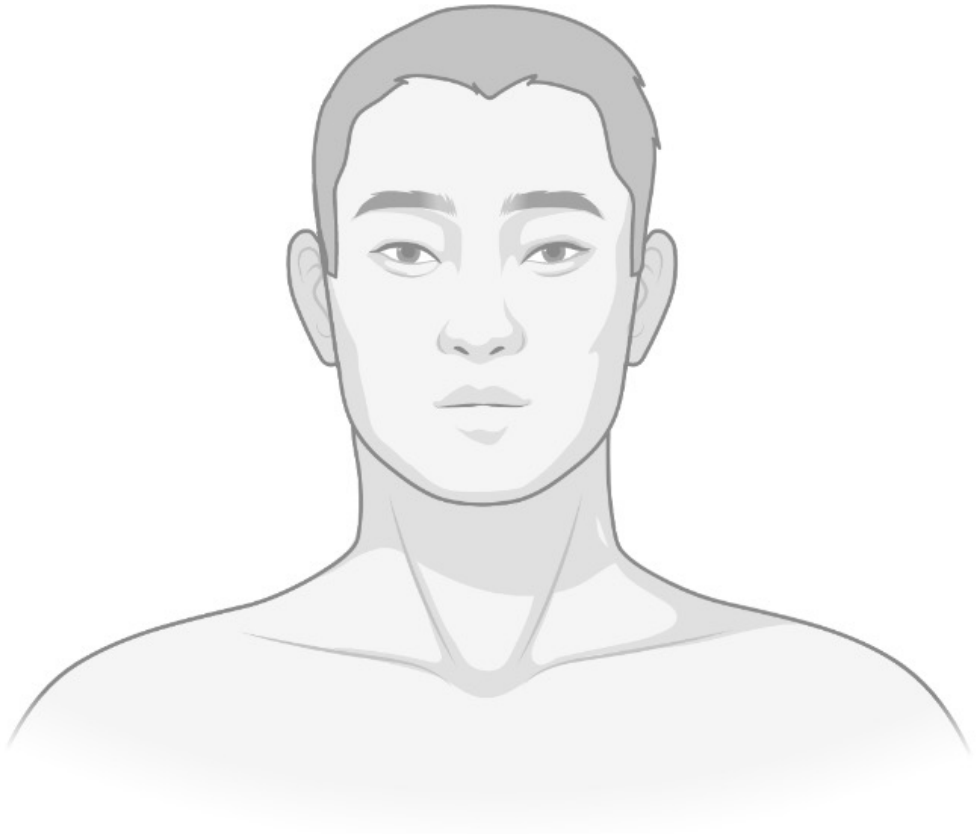
PROTOCOL GUIDANCE

For immediate insight on protocols for COVID using Humavir, go to slides 45-47.

For a genomic based rational for the care of individuals with COVID, review slides 3-44.

For guidance on the management of individuals with LONG HAUL COVID, go to slide 47.

POLYMORPHISMS



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- A1c = 5.4%
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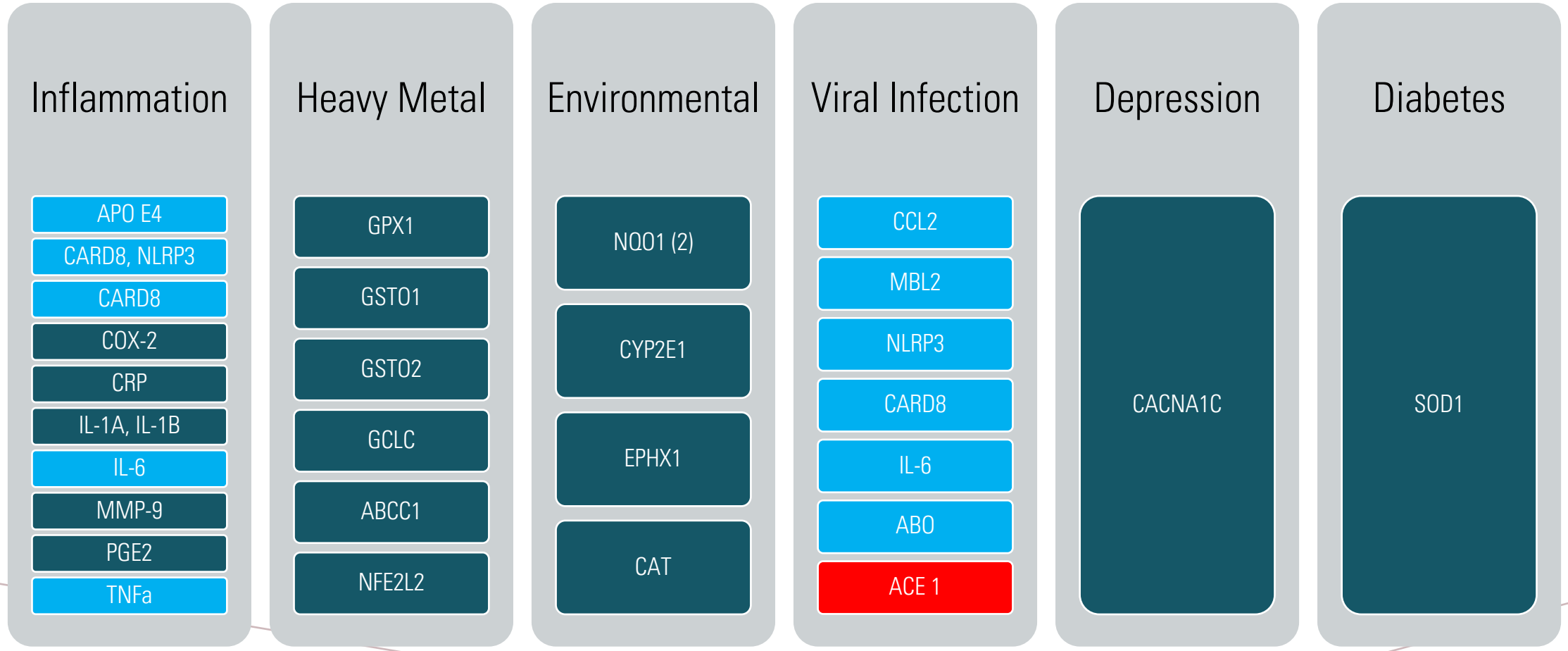
- TT= 962 ng/dL; FT= 172 ng/dL
- No autoimmune disease
- ApoE 3/3 (NOT ApoE4)

GENOMIC DRIVERS: INFLAMMATION & OXIDATIVE STRESS

.

Increased redox stress contributes to reduced antiviral host responses and increased virus-induced inflammation and apoptosis that ultimately drive cell and tissue damage and end organ disease. Gain, C., Song, S., Angtuaco, T., Satta, S., & Kelesidis, T. (2023). The role of oxidative stress in the pathogenesis of infections with coronaviruses. *Frontiers in microbiology*, *13*, 1111930.



"METABOLIC-OXIDATIVE STRESS INFLAMMATORY SPIRAL"

Thompson, E. A., et al. (2021). Metabolic programs define dysfunctional immune responses in severe COVID-19 patients. Cell reports, 34(11), 108863.

SARS-CoV-2

- (+) Subset of T cells with an altered metabolic profile are linked to disease severity and upregulation of voltage dependent anion channel 1 (VDAC1) expression.
- VDAC1: Part of a complex that regulates the exchange of ATP and ADP between the mitochondria and cytosol, associated with mitochondrial cell death signaling and autoimmunity
- T cell changes → prone to mitochondrial apoptosis → secondary lymphopenia

- Mitochondiral homeostatis
  - Essential for sustained killing by cytotoxic T cells

SARS-COV-2 CAUSES MITOCHONDRIAL DYSFUNCTION AND MITOPHAGY IMPAIRMENT

SHANG, C., LIU, Z., ZHU, Y., LU, J., GE, C., ZHANG, C., ... & LI, X. (2022). FRONTIERS IN MICROBIOLOGY, 12, 4159.

SARS-CoV-2 INFECTION

Membrane depolarization

Increased membrane permeability (TOM20)

Increased ROS production

DYSFUNCTION

↑ Pink1 and Parkin Protein

Pink1 mediated recruitment of p62

Mitophagy clock

MITOCHONDRIAL PRESERVATION

Viral mediated inhibition of p62 and LC3 binding

Inhibits emergence of autophagosomes

Zombification

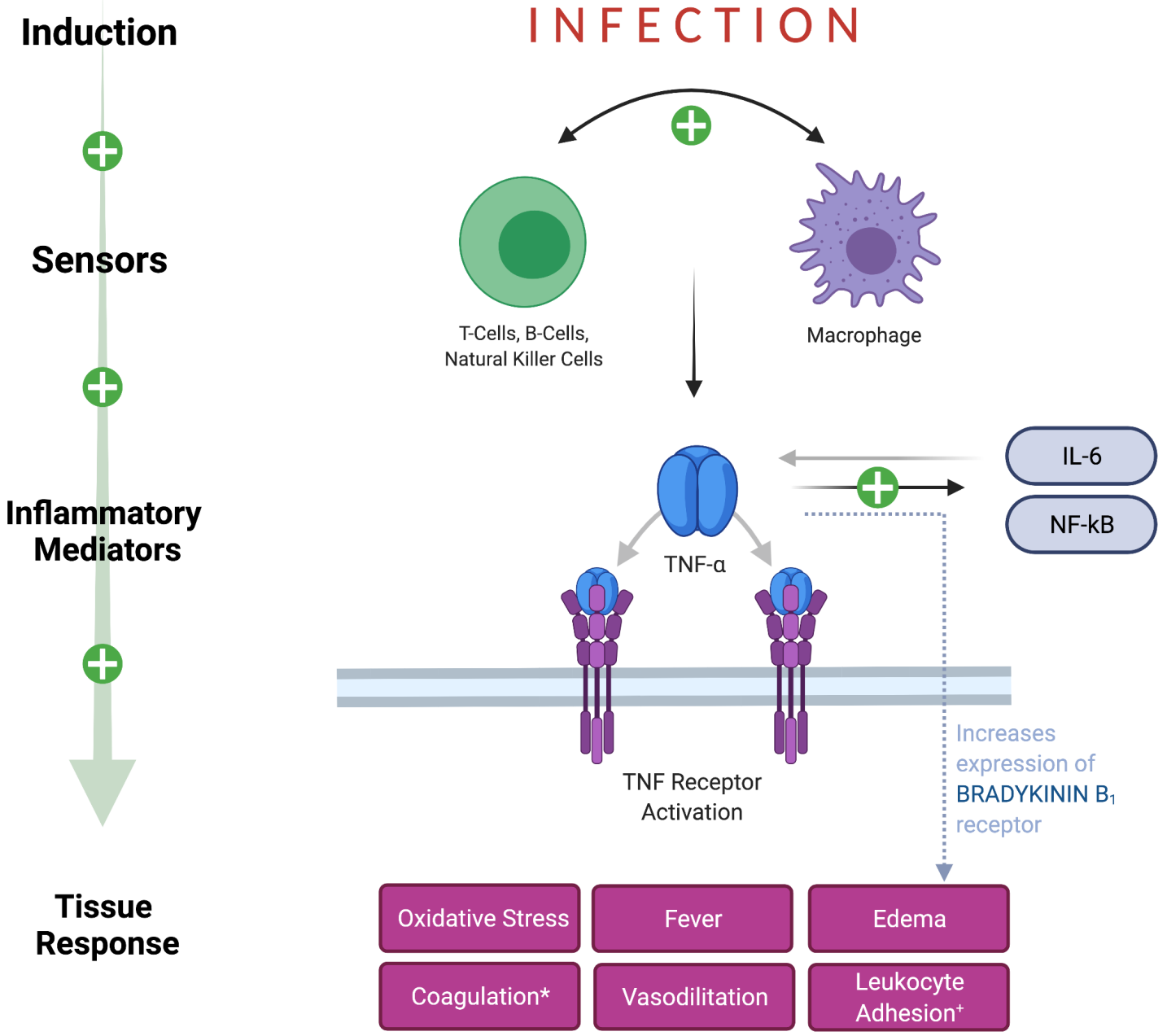
GENOMIC PATHWAYS

- INFLAMMATION
- THROMBOSIS
- VIRAL INFECTION

TNF-α

Risk SNPs:

- rs1800629
- rs361525
- rs1799724
- rs1799964



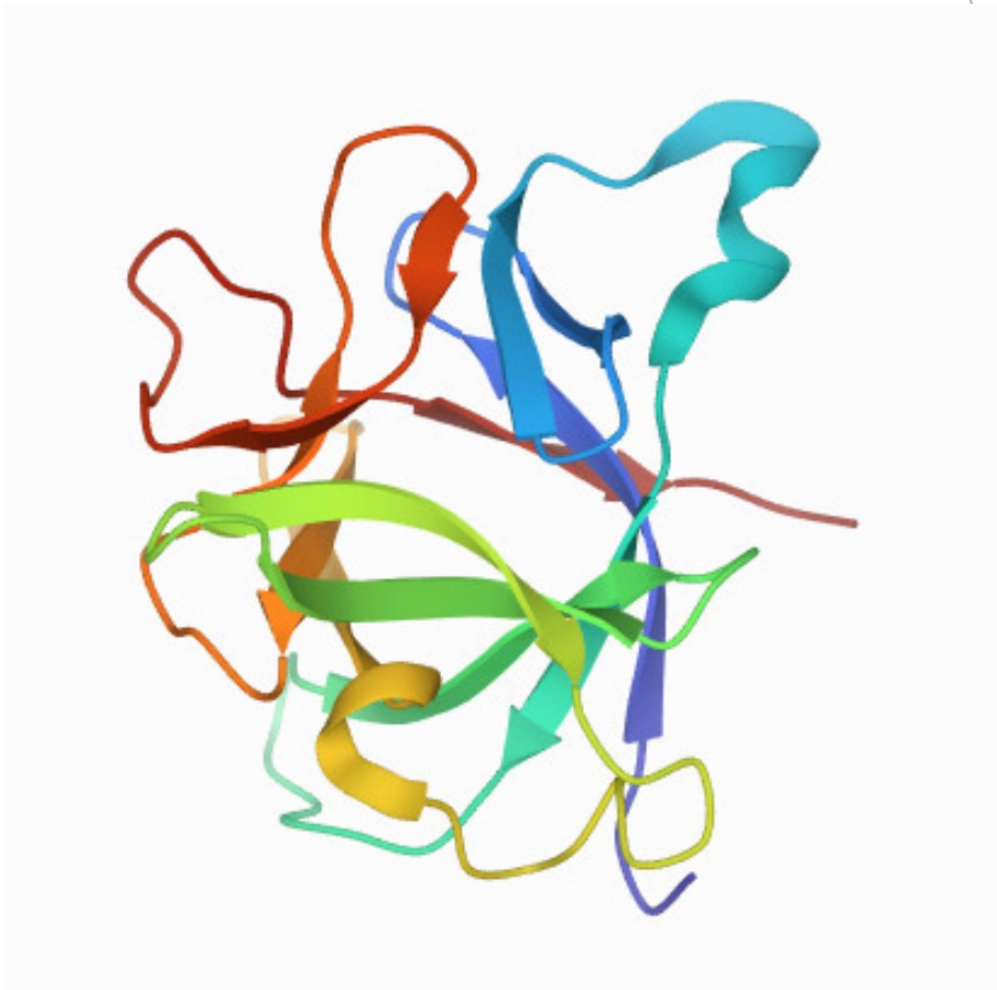
TUMOR NECROSIS FACTOR ALPHA

Risk SNP	Gene	Minor Allele	Patient Allele	Prevalence	Variant
rs1800629	TNF	A	AA	GG 2.6%	2

- TNF-α ▲
  - Baseline: Reactive cytokine that promotes additional inflammation
  - SNP: Higher incidence of infection and more serious disease. (Risk allele: A)
    - AA: 80% of hospitalized patients with Covid had severe symptoms.
    - GA: 41.7% of hospitalized patients with Covid had severe symptoms.
    - GG: 0% of hospitalized patients with Covid had severe symptoms.

IL-1β

- IL-1β ▲
  - 1 SNP = ~50% Caucasian population
  - Increased inflammatory response systemically
  - Crosses BBB
  - Produced by NF-kβ and released by inflammasomes
  - By definition - ▲IFN-γ
    - IFN-γ is an **important component of the innate antiviral response** and is predominantly produced by NK cells or innate lymphoid type 1 cells

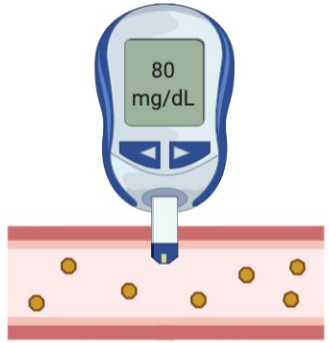


High-resolution three-dimensional structure of interleukin-1 beta in solution by three-and four-dimensional nuclear magnetic resonance spectroscopy. **PDB DOI:** 10.2210/pdb6I1B/pdb

IL6 - rs1800796

- IL6 SNP
  - OR: 1.52 ((ARDS) – homozygous SNP

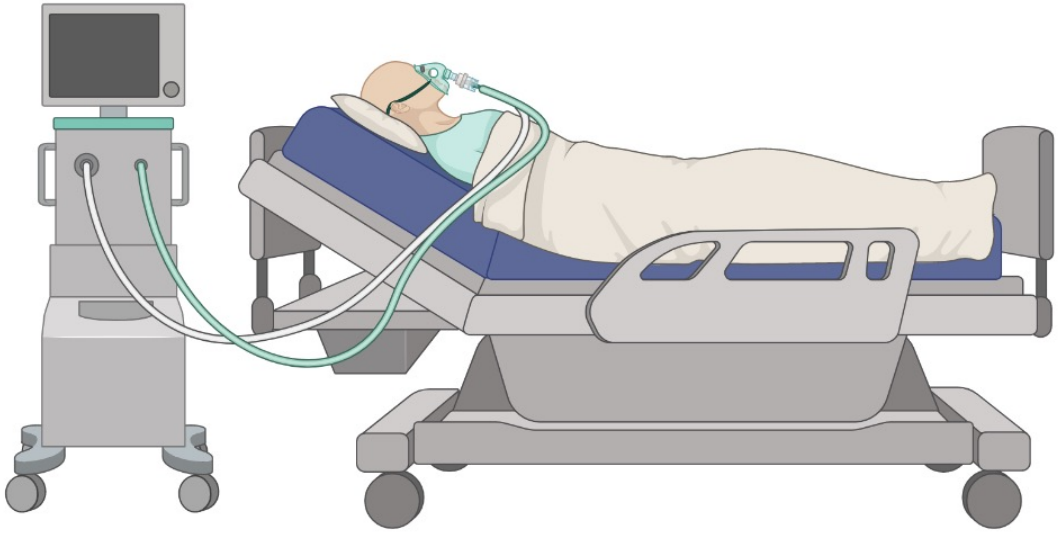
- SARS-CoV-2
  - Blood IL-6 level is highly correlated with the disease mortality and predicts the need for mechanical ventilation
  - SARS-CoV-2 induces release of IL-6 that is independent of SNPs
  - IL-6 and TNF-α serum levels are known to be significant predictors of disease severity and death.



▲OR: ACUTE RESPIRATORY DISTRESS SYNDROME

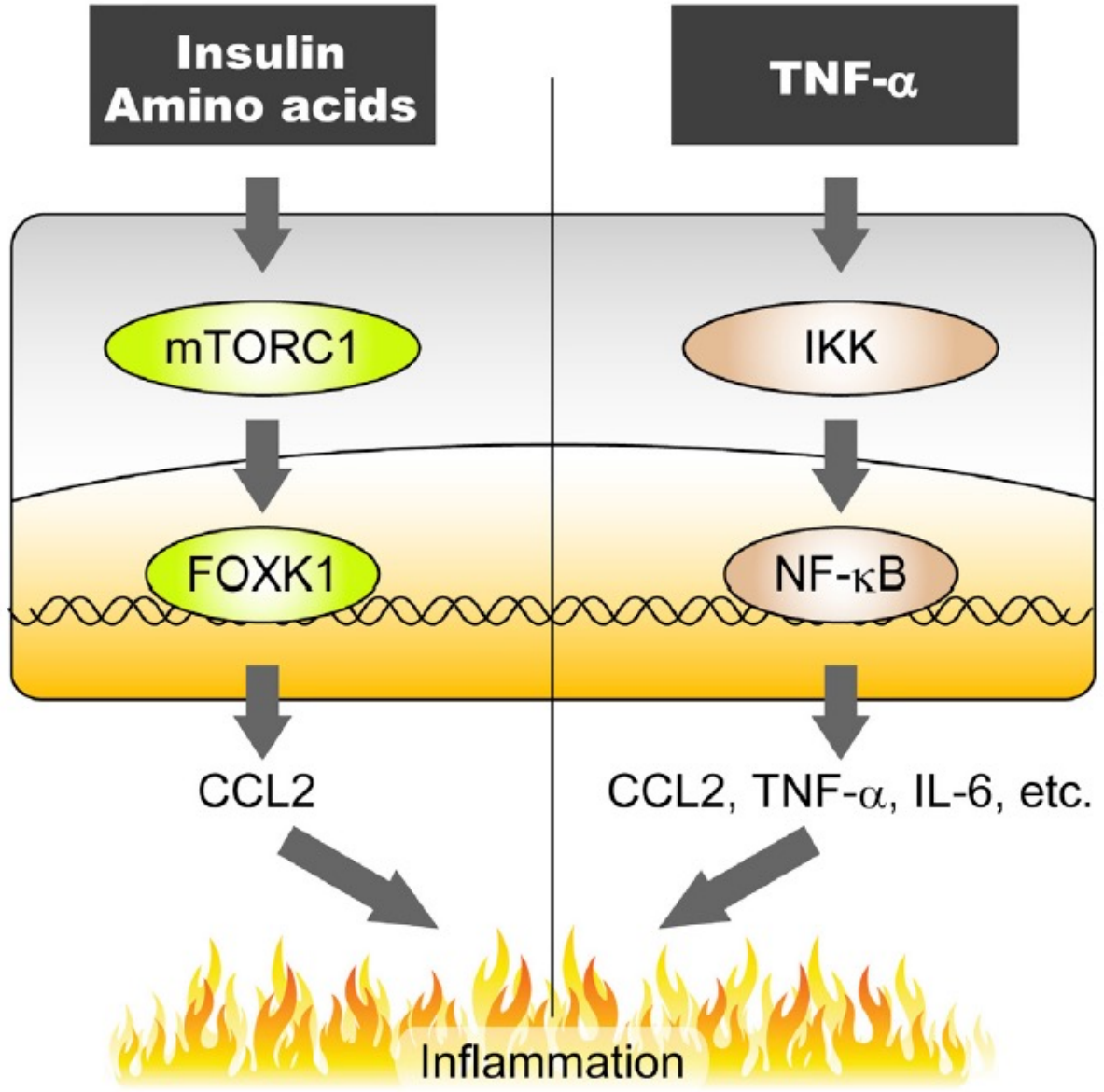
- MBL2 ▼
  - Baseline: Early warning system
  - Additive, w/ CCL2
  - OR = 2.88, heterozygous SNP

- CCL2 ▲
  - Baseline – Remove damaged tissue
  - Increased organ damage
  - Increased leukocyte infiltration of tissues
  - Trojan horse effect – wider viral dissemination
  - OR = 1.58, homozygous SNP



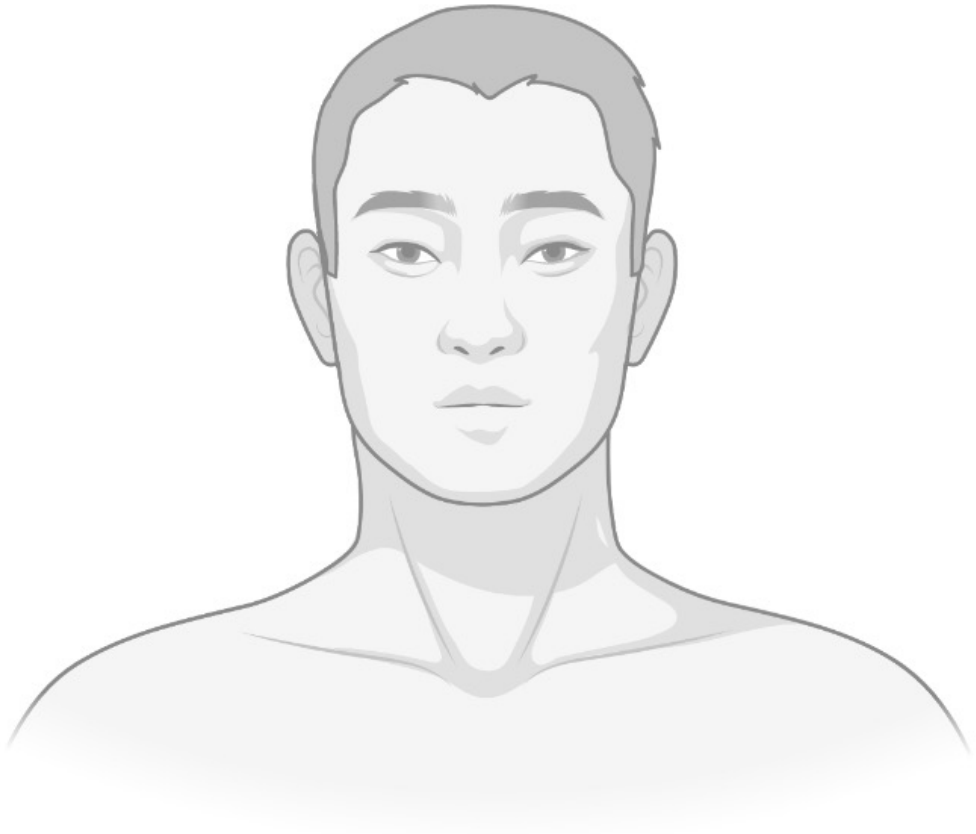
NONCANONICAL PATHWAY FOR REGULATION OF CCL2

NF-KB BYPASS



INFLAMMATORY MODULATION

- NLRP3 ▲
  - Increased inflammatory response
  - Activation - ▲IL-1β
  - Activated by SARS-CoV-2
- CARD8 ▼
  - Part of NLRP3 inflammasome complex
  - ▲ NF-kβ
  - ▲ Caspase 1
  - Increased inflammatory response
  - Difficulty modulating inflammasomes



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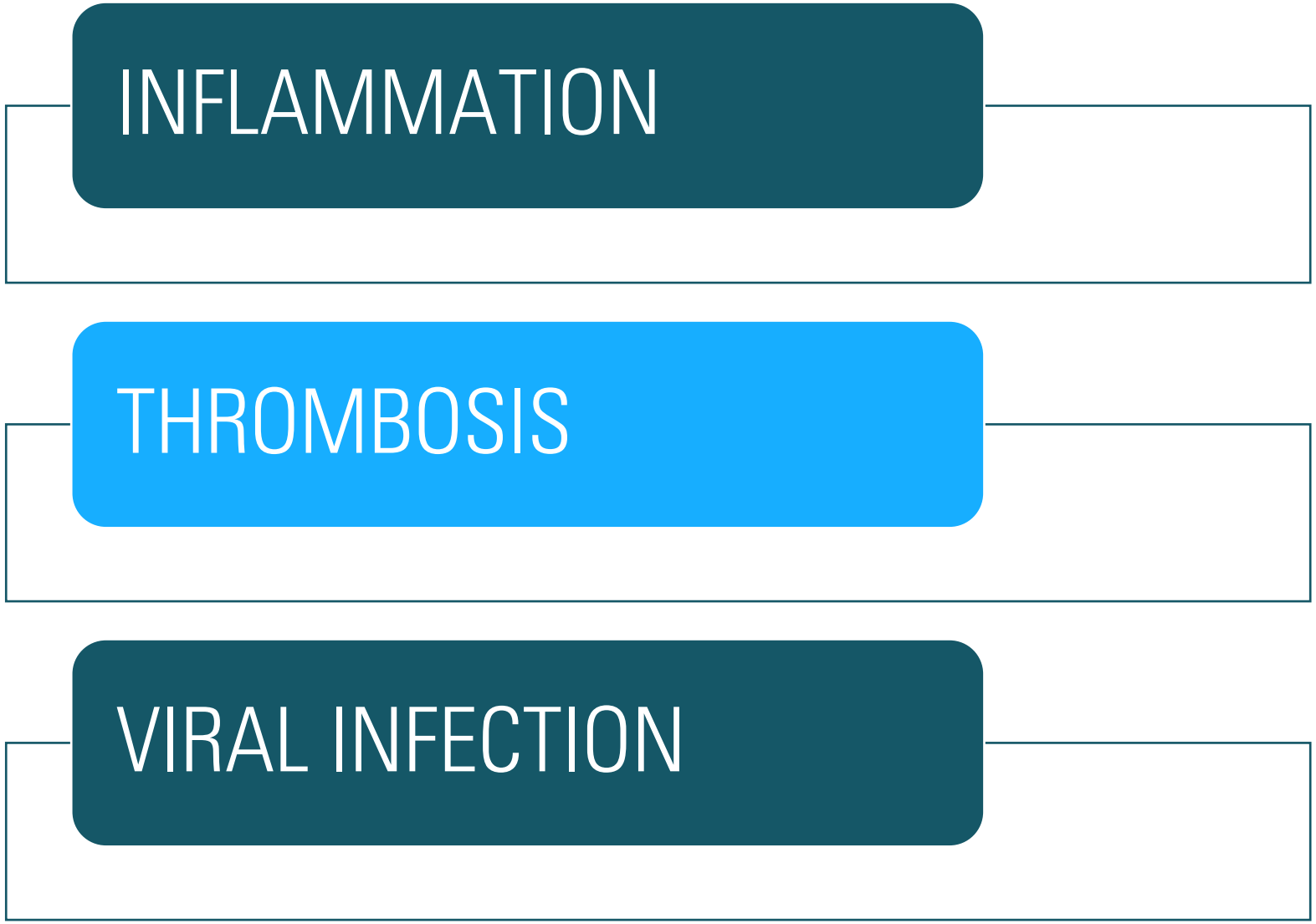
  - IL-1B

GENOMIC PATHWAYS



HYPERCOAGULABLE

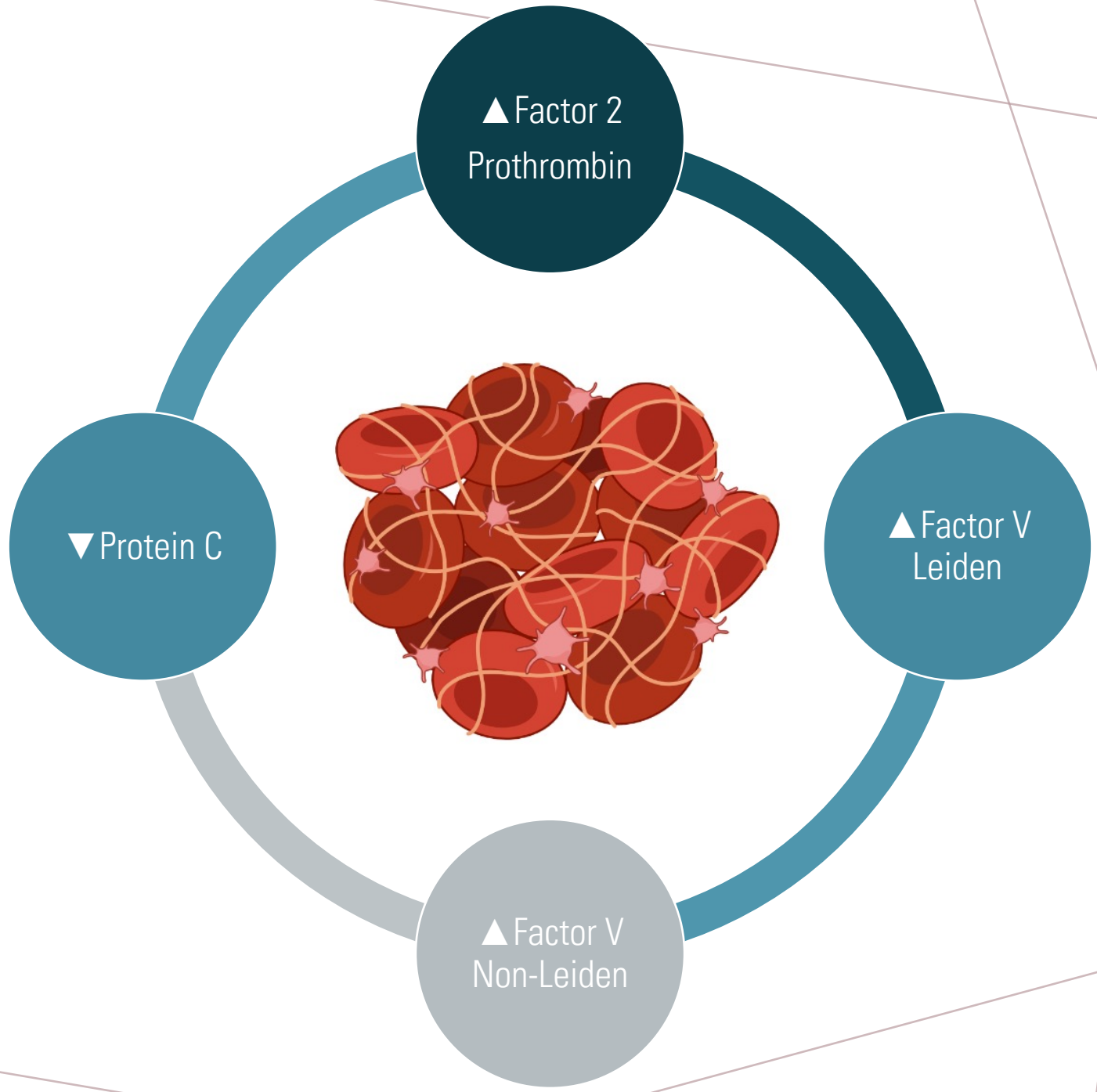
OR:

F2: 5.5, central venous thrombosis

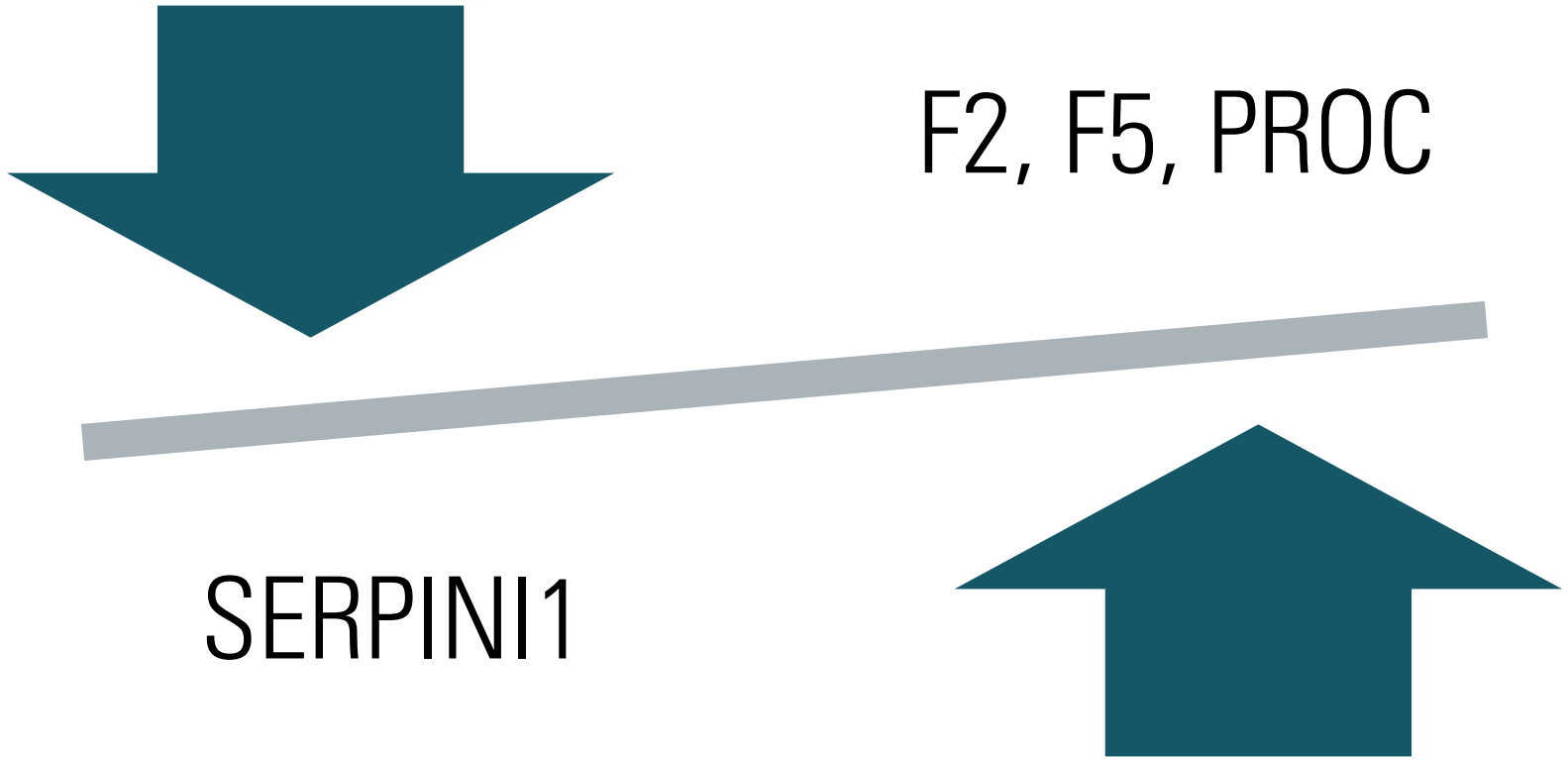
F5 Leiden: 50x (homozygous, lifetime)

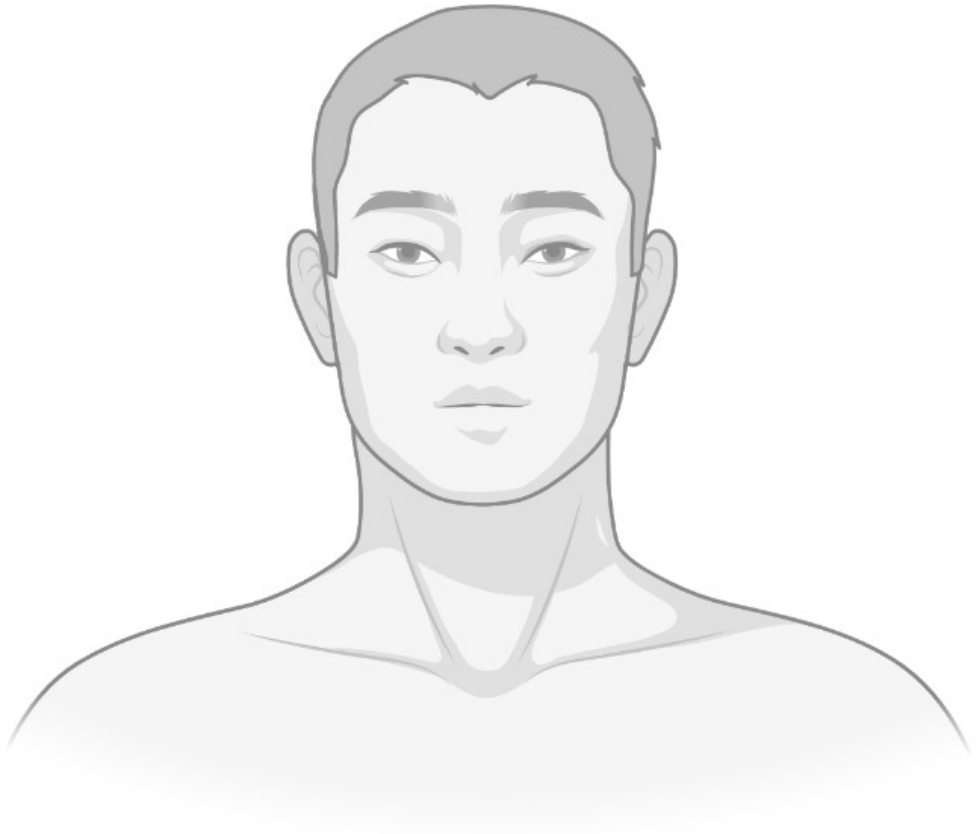
F5 – Non-Leiden: increased risk of CHD (OR = 2.63) and stroke (OR = 13.51) in women

PROC = NOT LINKED TO A DEFICIENCY – increased risk of stroke, men & women



COUNTERBALANCE





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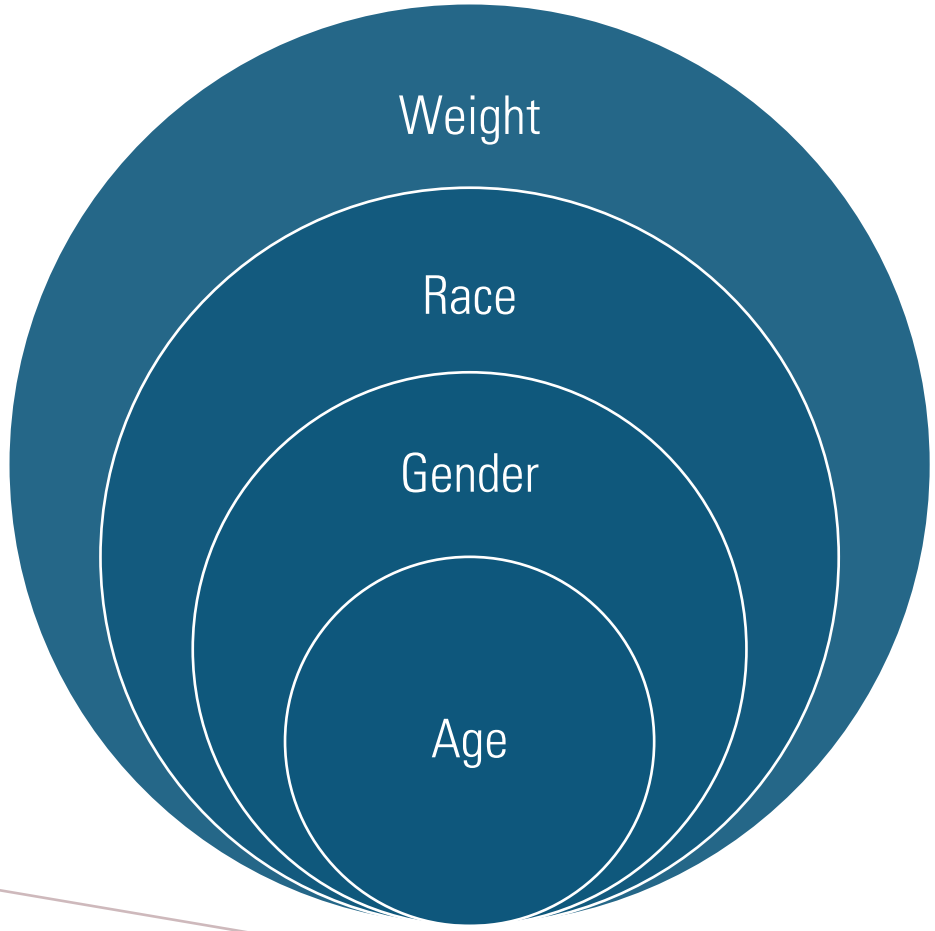
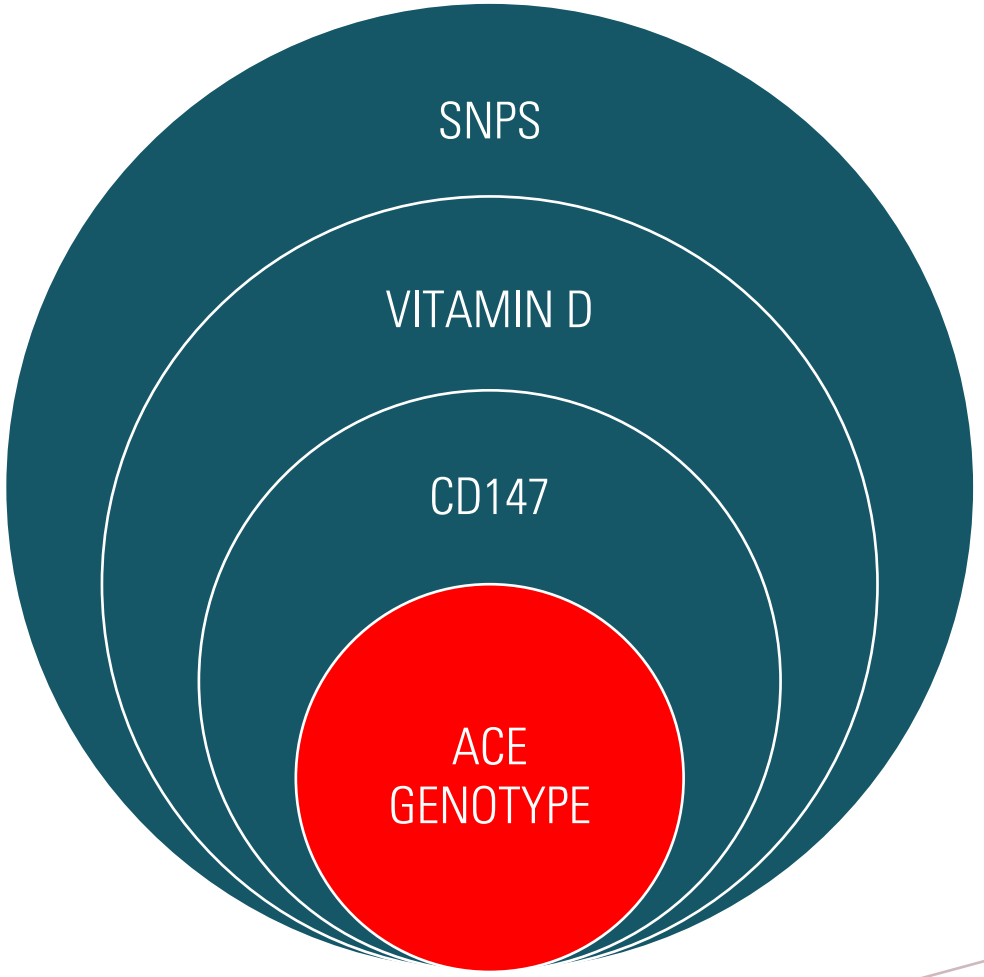
  - Factor V Non-Leiden
  - Protein C

GENOMIC PATHWAYS

- INFLAMMATION
- THROMBOSIS
- VIRAL INFECTION

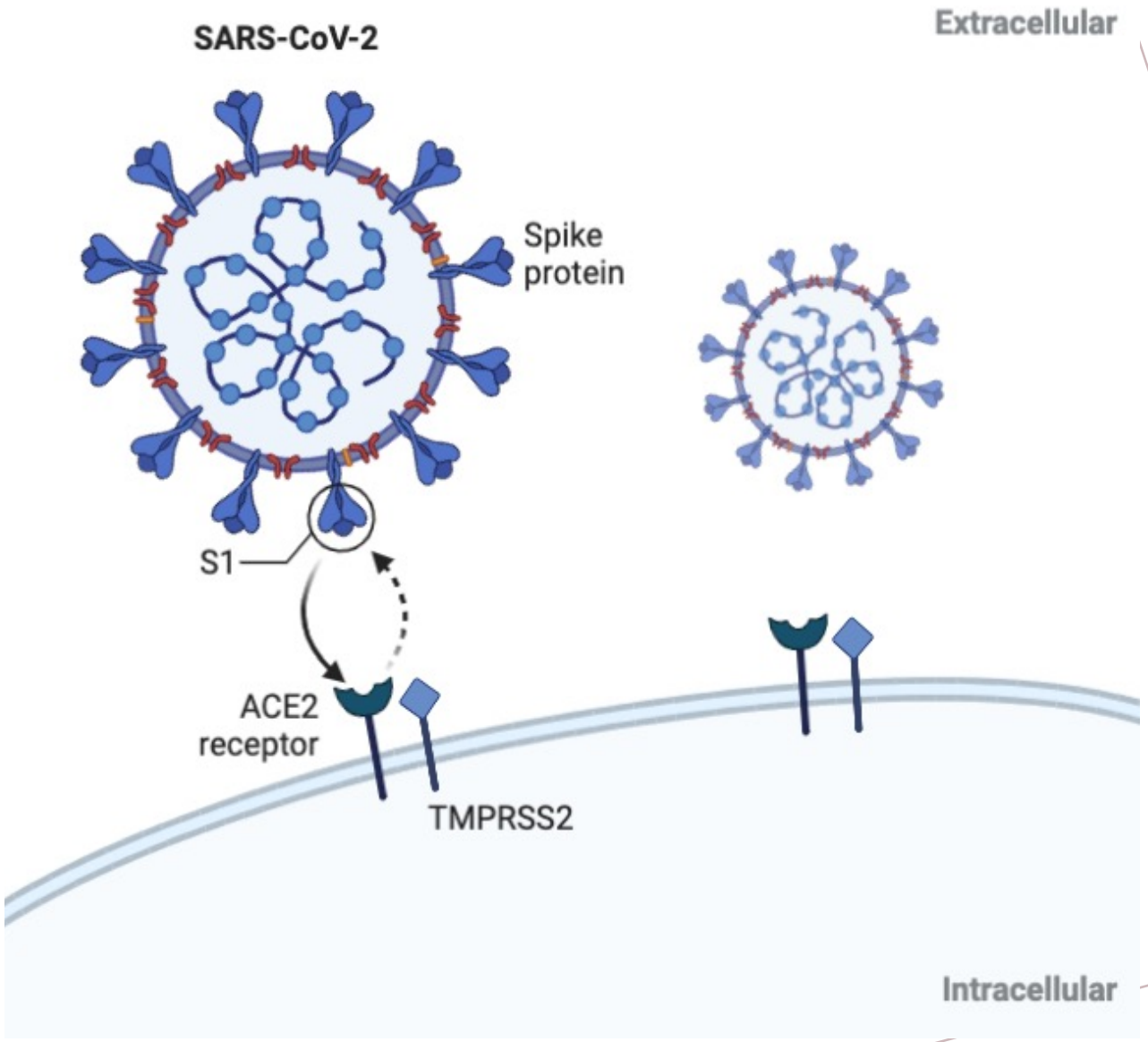
FROM COVID PHENOTYPE TO ACE GENOTYPE





ACE2 RECEPTOR

- Receptor density: Nasal epithelial cells > lung T2 aveolar epithelial cells > GI and heart
- Higher ACE2 Receptor Density: Asian than Caucasian & AA
- Smoking – increases expression ACE2 in lung epithelium



ACE1 GENOTYPE, CHROMOSOME 17

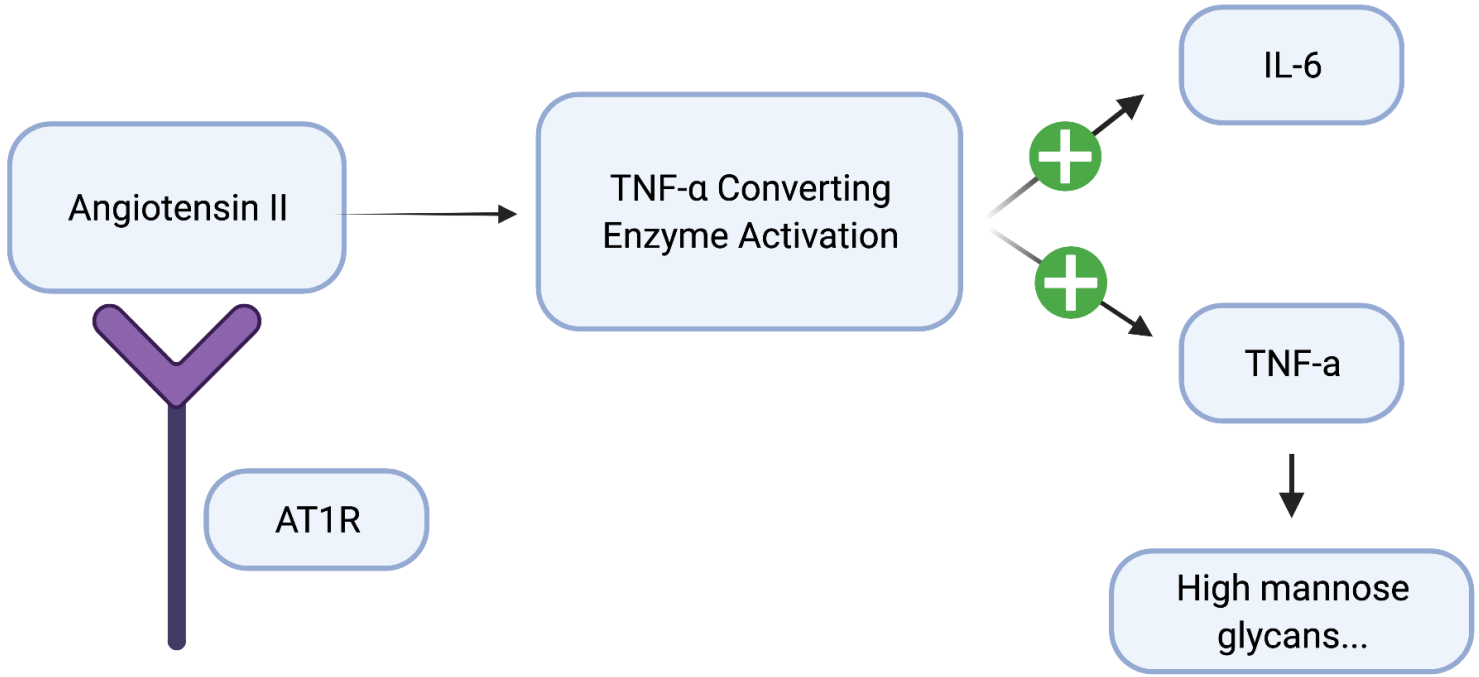
Sarangarajan R, Winn R, Kiebish MA, Bountra C, Granger E, Narain NR. Ethnic Prevalence of Angiotensin-Converting Enzyme Deletion (D) Polymorphism and COVID-19 Risk: Rationale for Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers. J Racial Ethn Health Disparities. 2021;8(4):973-980.

- ACE DD (Risk) vs. ACE II (vs. DI)
- SARS-CoV2 & ACE DD SNP, overstimulation of AT1-R
  - Reduction in ACE2 (due to overactivation of RAS), increase ACE/ACE2 , increase in angiotensin II.
  - Vasoconstriction
  - Sodium & water retention
  - Cell proliferation
  - Increased ROS production
  - Increased inflammation
  - Fibrosis
  - Organ damage

SARS-COV2, TNF-α & IL-6

- TNF-α & IL-6 – most critical cytokines to COVID-19 severity

  - both mediate MBL and T-helper lymphocytes (Th-17, marker of autoimmune disease) response
  - IL-6 & TNF-α increase CD-147 receptors



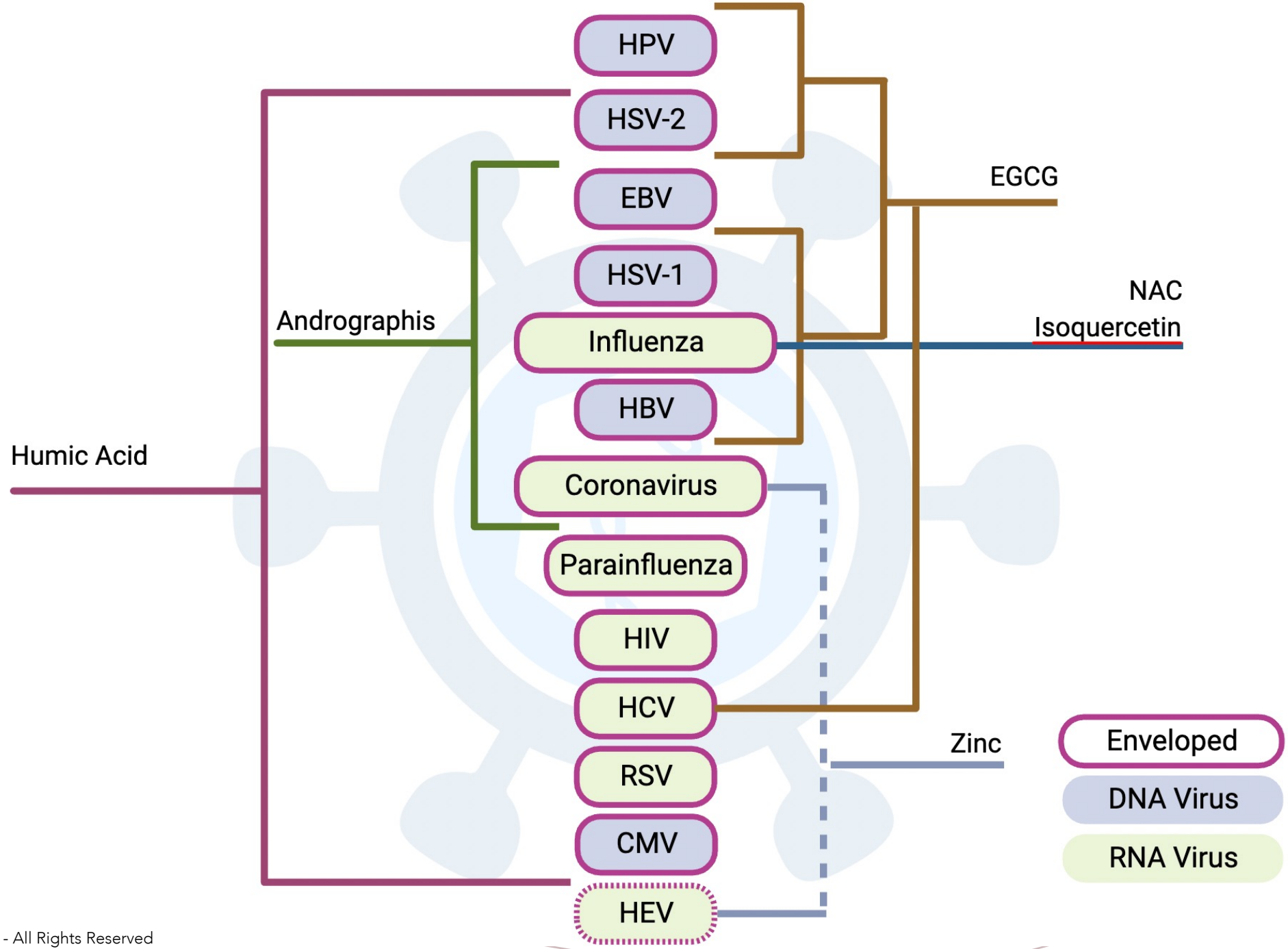
- COVID-19 directly stimulates release of IL6.

ALLELE FREQUENCIES – ACE DD

POPULATION	I	D
BAKA PYGMY, GABON	0.14	0.86
MOROCCAN	0.29	0.71
AFRICAN AMERICANS	0.43	0.57
ENGLAND	0.45	0.55
FRANCE	0.42	0.58
EAST ASIA	0.63	0.29

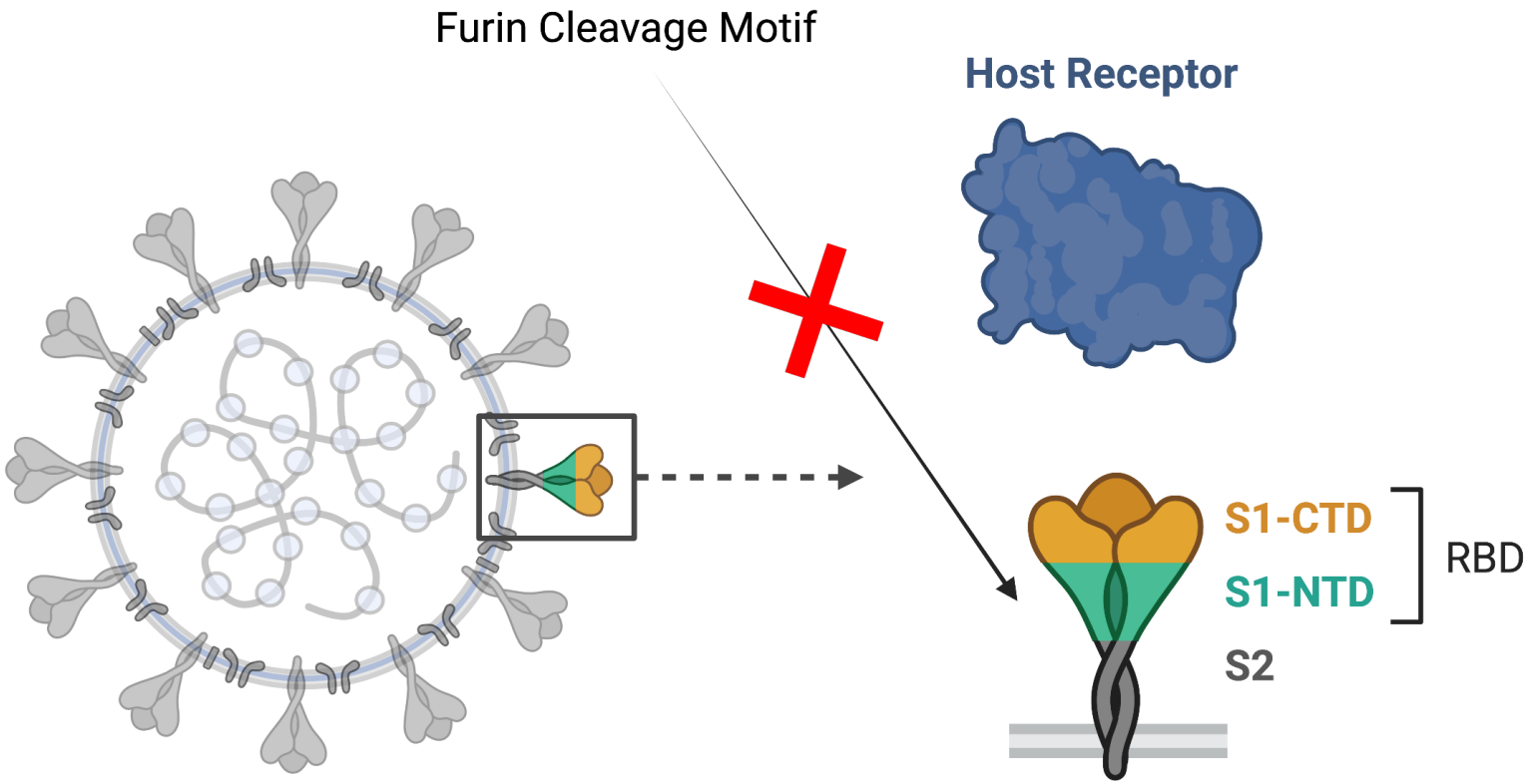
SOLUTIONS

FUNCTIONAL TREATMENT OPTIONS



ANDROGRAPHIS

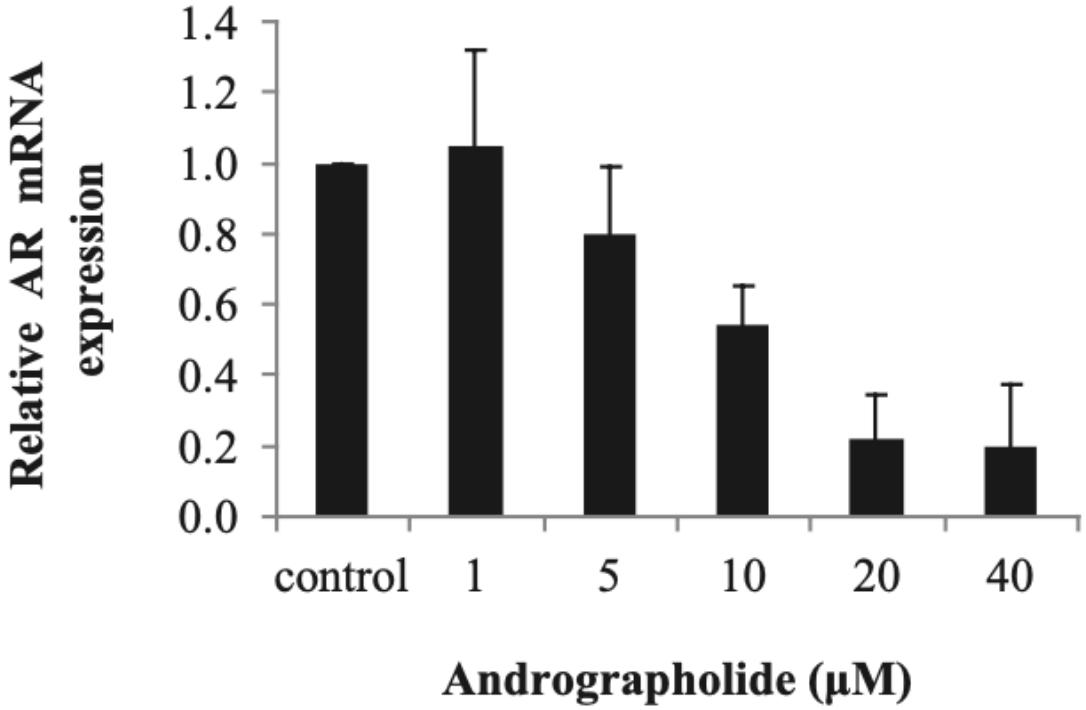
FURIN PROTEASE INHIBITOR – BLOCKS CLEAVAGE OF S1/S2 & MEMBRANE FUSION

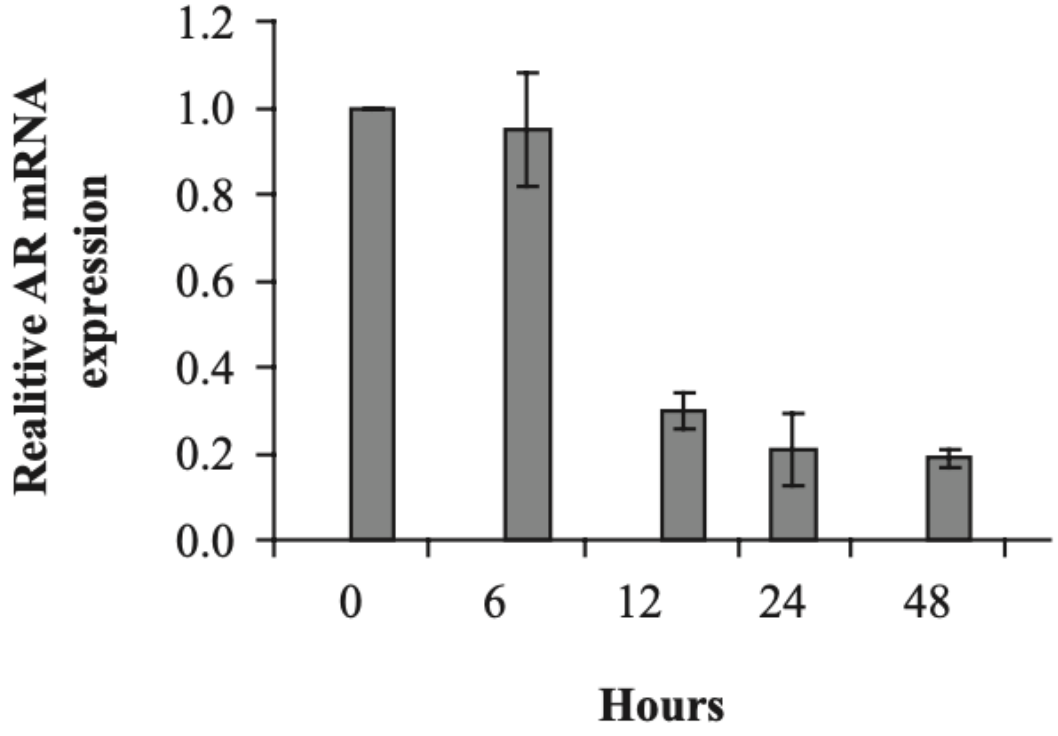


LIU, C., NADIMINTY, N., TUMMALA, R., CHUN, J. Y., LOU, W., ZHU, Y., SUN, M., EVANS, C. P., ZHOU, Q., & GAO, A. C. (2011). **ANDROGRAPHOLIDE TARGETS ANDROGEN RECEPTOR PATHWAY IN CASTRATION-RESISTANT PROSTATE CANCER.** GENES & CANCER, 2(2), 151–159. HTTPS://DOI.ORG/10.1177/1947601911409744

Andrographolide is able to **down-regulate AR expression** at both mRNA and protein levels, prevents its nuclear translocation, and inhibits transactivation of its target genes.

LIU, C., NADIMINTY, N., TUMMALA, R., CHUN, J. Y., LOU, W., ZHU, Y., SUN, M., EVANS, C. P., ZHOU, Q., & GAO, A. C. (2011). **ANDROGRAPHOLIDE TARGETS ANDROGEN RECEPTOR PATHWAY IN CASTRATION-RESISTANT PROSTATE CANCER.** GENES & CANCER, 2(2), 151–159. HTTPS://DOI.ORG/10.1177/1947601911409744





DUAL FUNCTION

ANTI-VIRAL & ANTI-INFLAMMATORY

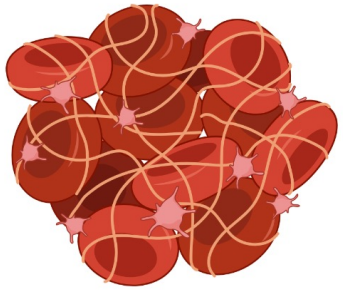
MOLECULE	CYTOKINE	INFLAMMASOME
Andrographis	CCL2 TNF-α IL-1β IL-6	NLRP3
EGCG	IL-1β (conflicting data) TNF-α (conflicting data)	NLRP3
Humic Acid 95%	TNF-α	
Quercetin	IL-1β TNF-α (Augmented by ascorbic acid)	NLRP3
Zn*	IL-1β **IL-6** IL-2 **TNF-α**	

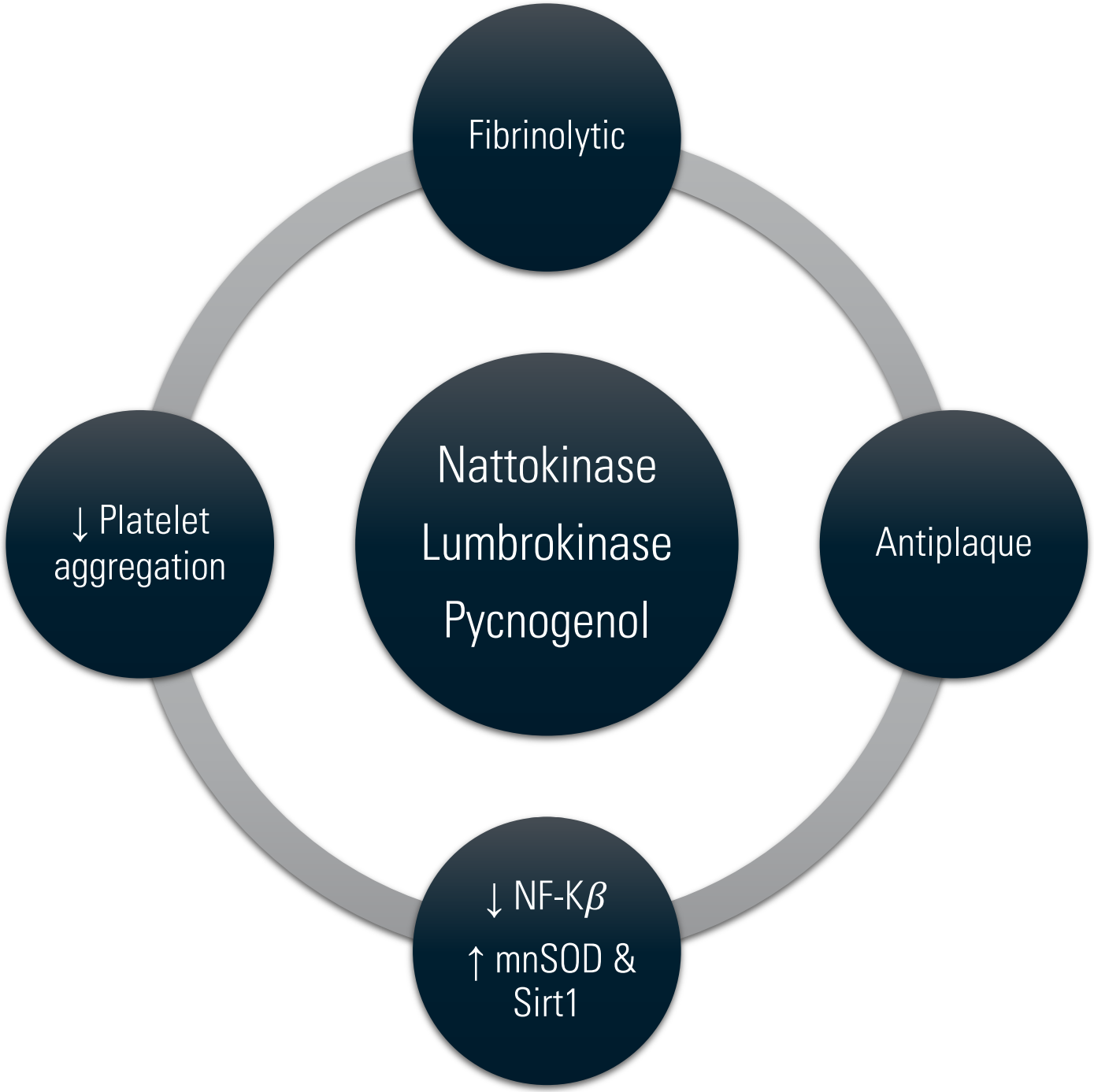
TARGETED FUNCTION

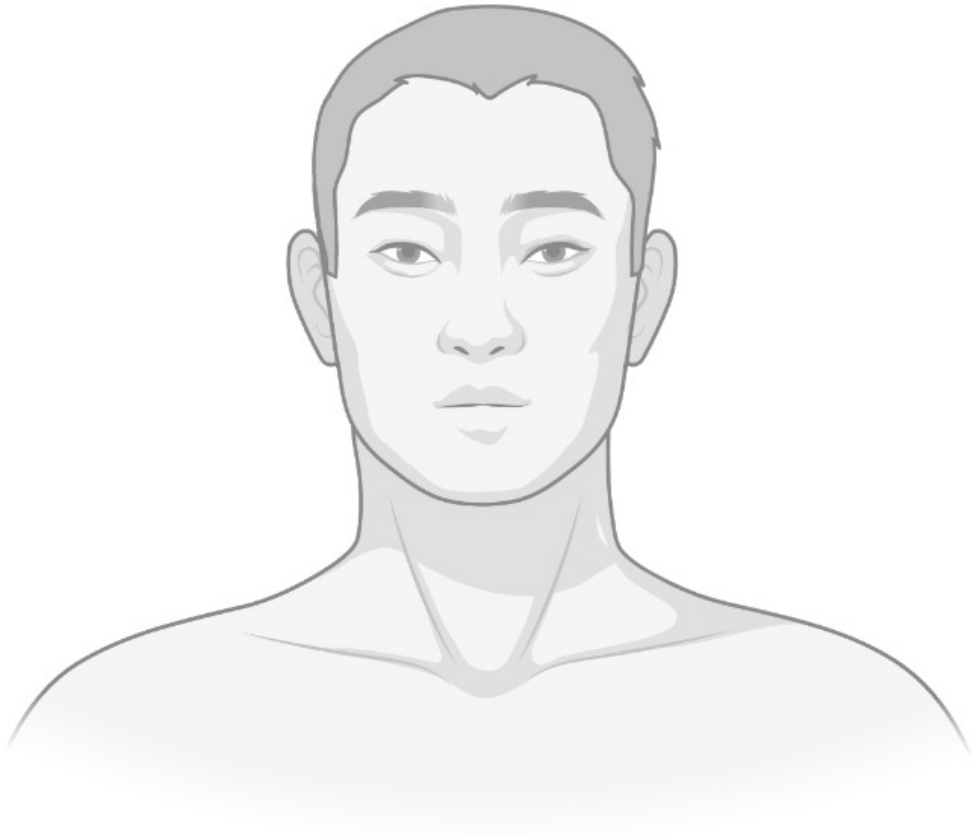
ANTI-INFLAMMATORY

MOLECULE	CYTOKINE	INFLAMMASOME
Astralagus	CCL2 TNF-α IL-1β IL-6	NLRP3
Resolvins	IL-1β	CARD8 NLRP3

FIBRINOLYTICS







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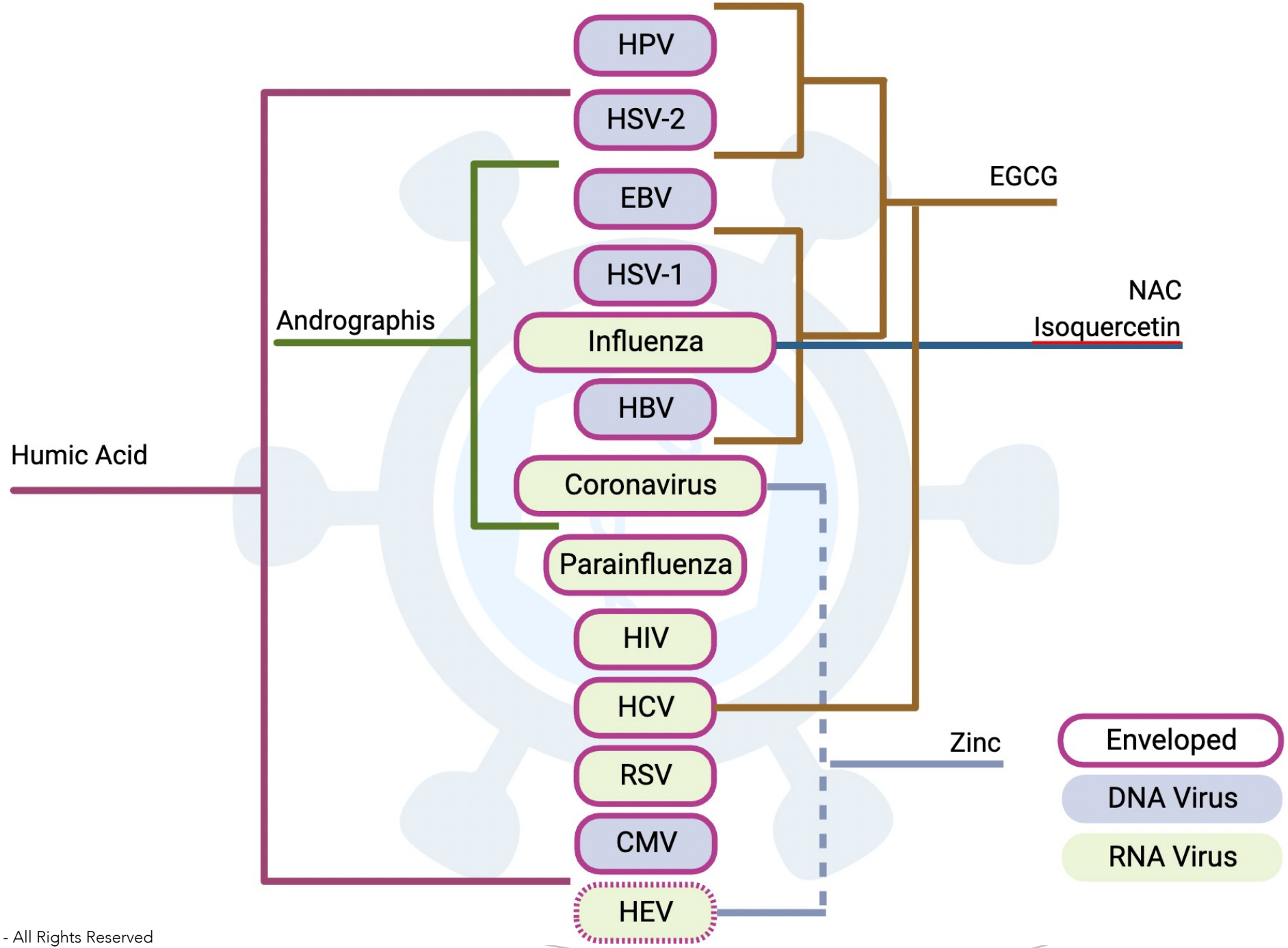


VIRACID

Supplement Facts

V6

Serving Size 2 Capsules
Servings Per Container 30

	Amount Per Serving	% Daily Value
Vitamin A (from 15,000 IU as Palmitate, Natural Beta Carotene)	4,500 mcg	500%
Vitamin C (as Ascorbic Acid USP, Acerola Fruit Juice Concentrate Powder)	300 mg	333%
Vitamin B12 (as Methylcobalamin)	2.5 mcg	104%
Pantothenic Acid (as d-Calcium Pantothenate USP)	10 mg	200%
Zinc (as Albion® Minerals Zinc Bisglycinate Chelate)	4 mg	36%
Astragalus *(Astragalus membranaceus)* Root Extract	250 mg	*
European Elder (*Sambucus nigra*) Berry Extract (Standardized to contain 13% Anthocyanins)	250 mg	*
Andrographis (*Andrographis paniculata*) Leaf Extract (Standardized to contain 30% Andrographolides)	200 mg	*
Echinacea purpurea Extract (Flowering Aerial Parts) (Standardized to contain 4% phenols)	100 mg	*
L-Lysine Hydrochloride USP	100 mg	*
Acerola Fruit Juice Concentrate Powder (Standardized to contain 17% Vitamin C)	25 mg	*

* Daily Value not established.

HUMIC ACID (HA) VS. HUMAVIR

HA from Advanced Humeomics' reserves, Humavir = Enhnanced HA

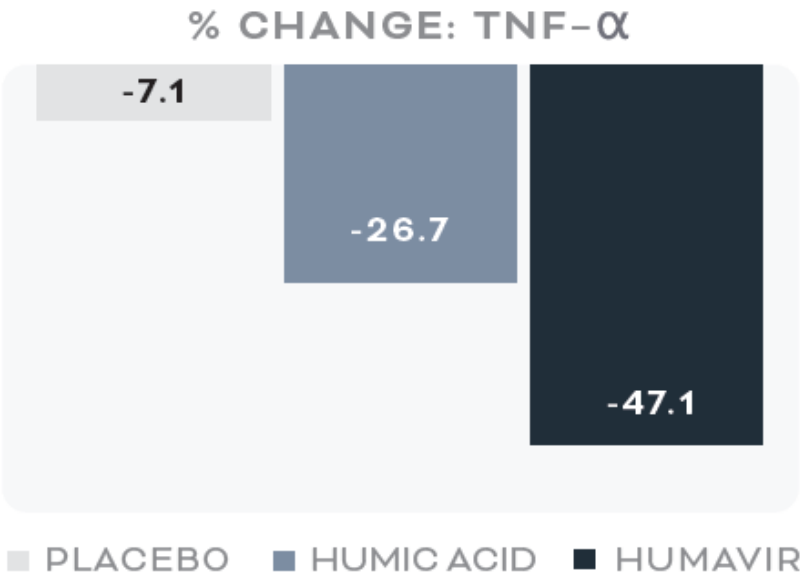
INFLUENZA CLINICAL STUDY

WEEK 2, PERCENT IMPROVEMENT

SYMPTOM	HUMIC ACID n = 19	PLACEBO n = 18	EHNANCED HUMIC ACID n = 10	PLACEBO n = 10
Cough	61.9	36.8	79.2	32.8
Fever	91.7	81.8	93.4	79.2
Myalgia / arthralgia	86.4	62.5	90.5	60.7
Chills	91.7	66.7	92.6	59.5
Fatigue	80.0	54.5	83	51
Rhinorrhea	66.7	62.5	68.9	59.5

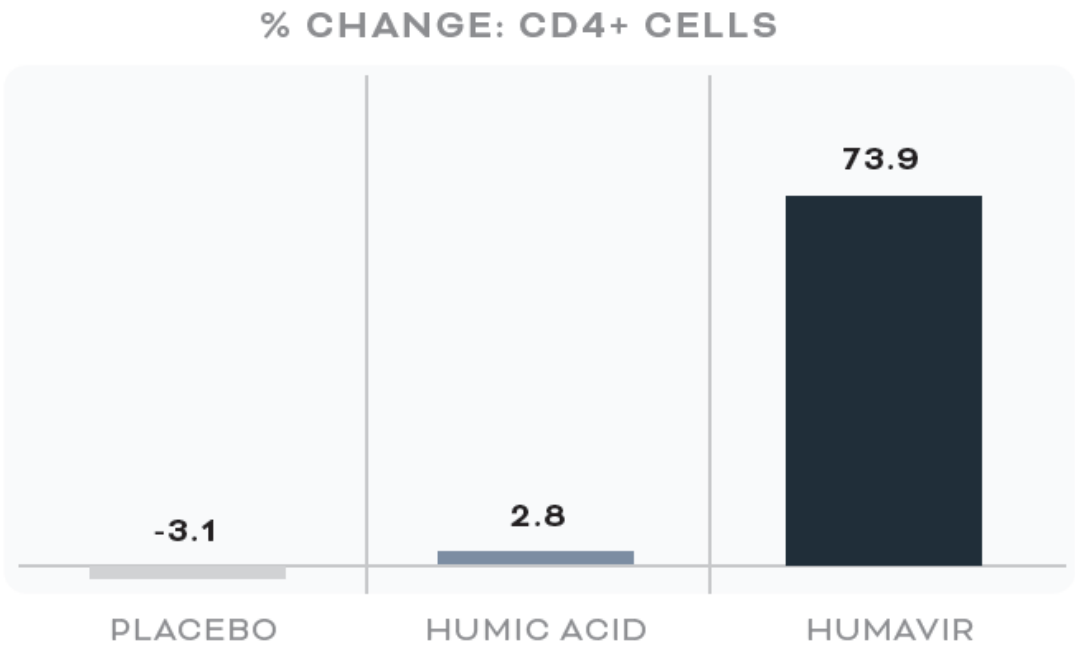
Tumor Necrosis Factor Alpha (Influenza)

Tumor necrosis factor alpha (TNF-α) is a protein made by activated immune cells. At moderate concentrations, TNF-α promotes an inflammatory response. Blood samples of study participants revealed a greater decrease in TNF-α concentrations in those using Humavir vs. humic acid.



CD4 Immune Cells (Influenza)

CD4+ cells may be regarded as a benchmark of immune system integrity. Blood samples of study participants revealed a greater increase in CD4+ count in study participants using Humavir versus humic acid alone.



Visual Analog Scale (Influenza)

The visual analog scale is a validated psychometric response scale that is often used to assess subjective characteristics or impressions that cannot be directly measured.

Participants who received product in the two treatment groups, humic acid and Humavir, opined that their improvement at the 7 and 14-day assessment touch points was more robust than either placebo group. In addition, the self-assessments of participants in the Humavir study group were more positive than those using humic acid alone.

PERCENT IMPROVEMENT

Day	Humic Acid	Placebo	Humavir	Placebo
7	64%	54%	82.7%	35.9%
14	107%	76%	120.8%	65.8%

Time Kinetics of Viral Clearance & Resolution of Symptoms (SARS-CoV-2)

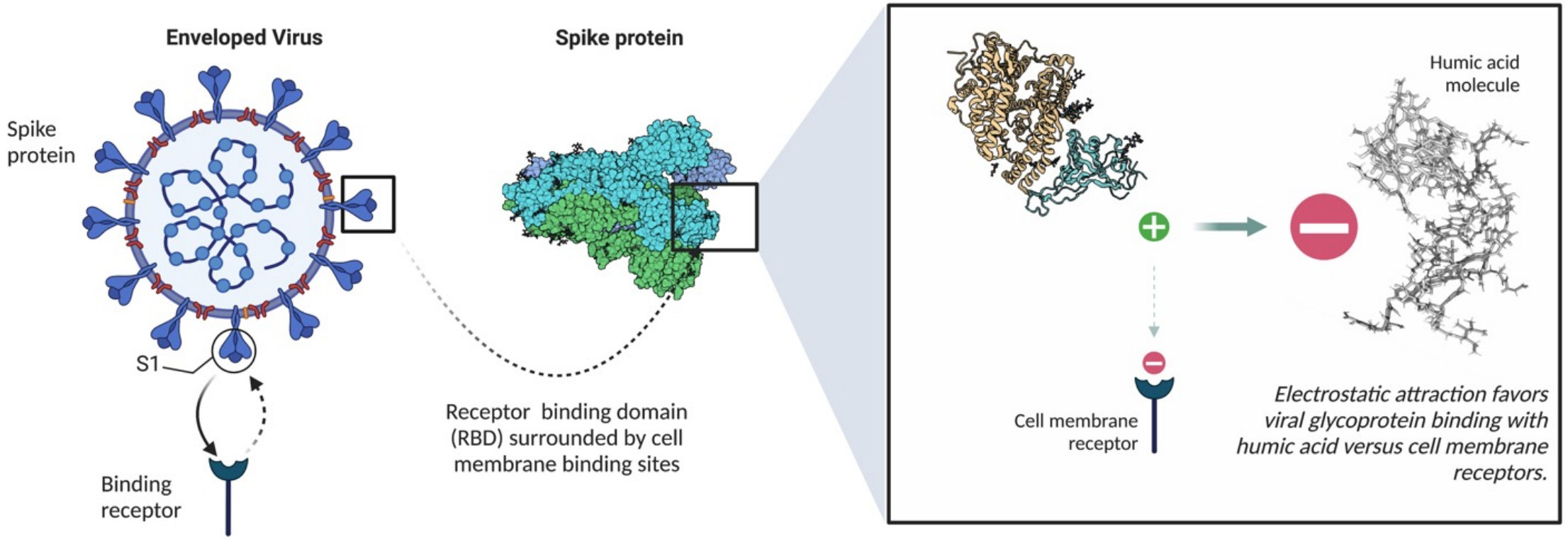
An open label, non-randomized trial with 20 adults was performed to 2020 to assess the efficacy of Humavir versus SARS-CoV-2. Outcome data was compared to Chang, et alia's publication on viral clearance and symptom resolution.

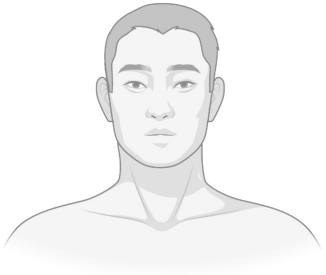
						SYMPTOMS, N (%)				TIME KINETICS, DAYS			
	Date	n	Age (years)	Asymptomatic Individuals	Care Setting**	Cough	Dyspnea	Fever	Nausea/ Emesis	Elapsed time (days), onset to resolution of symptoms	Elapsed time (days), start of treatment to symptom resolution	Days from virus positivity to negativity	Individuals, virus positive after symptom resolution
PLA General Hospital Chang, et. al.	Jan-Feb 2020	16	35.5 (24-43)	0	Hospital	14 (87)	2 (12.5)	14 (87.5)	2 (12.5)	8 (6.5-11.5)	-	5.5 (4-8)	8 of 16
Humavir	Mar-Apr 2020	20	47.4 (19-72) 120.8%	6	Ambulatory	12 (86)	3 (21)	13 (93)	9 (64)	-	5.2 (4-7)*	4.0 (3-6), age 24-43	4.35 (2-7), age 19-72

* Asymptomatic individuals removed ** All patients were hospitalized based on Chinese policy rather than depth of illness.

Figure 2: Binding Mechanism of Humic Acid with Spike Proteins

Net negatively charged humic acid binds to positively charged viral glycoproteins to inhibit viral binding to target cell membrane receptors.





CARE

VIRAL INFECTION

INFLAMMATION

THROMBOSIS

VITAMIN D

Viracid®
Humavir®

Boluoke®

TREATMENT CONCEPTS

HYBRID

- PAXLOVID
- HUMAVIR

SILO 1

- VIRACID
- HUMAVIR

SILO 2

- BOLUOKE
- SPM ACTIVE

SILO 3

- MITOCHONDRIAL SUPPORT

DOSING

HUMAVIR + VIRACID COMBINATION

For **HIGH RISK** exposure (husband or family member gets COVID), take 2 Viracid twice a day and 1 Humavir twice a day.

For **HIGH RISK EVENTS**, like a gathering, take 1 Humavir three times a day the day before, day of, and day after the exposure.

For **TREATMENT**, take 1-2 Humavir 3x/ day x 5-7 days and 2 Viracid three times a day, and then continue 1 Humavir 2-3x day for an additional week.

For **AGGRESSIVE SYMPTOMS**, start SPM Active by Metagenics. Take 2-3 softgels three times daily. SPM Active is an additional anti-inflammatory.

To restore a sense of taste and smell, consider Boluoke, 2 capsules 2-3 times daily.

LONG HAUL COVID

Consider work of Patterson, *et alia*, or a combination of approaches.

Rationale:

- Patterson, B. K., Guevara-Coto, J., Yogendra, R., Francisco, E. B., Long, E., Pise, A., ... & Mora-Rodríguez, R. A. (2021). Immune-based prediction of COVID-19 severity and chronicity decoded using machine learning. Frontiers in immunology, 12, 2520

Laboratory:

- https://theradiancediagnostics.com/order-tests/chronic-covid/

Treatment Center

- https://www.covidlonghaulers.com/

PUTTING IT ALL TOGETHER

- Clinical genomics improves clinical efficiency and patient outcomes.
- There is both a genomic signature to viral susceptibility and a genomic map to optimizing care.
- Safe and effective, non-prescription based treatment strategies are available.

REFERENCES

FOR A COMPLETE LIST OF THE 50+ REFERENCES FOR THIS PRESENTATION PLEASE WRITE TO DAVID@HUMEO.IO

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- Sarangarajan R, Winn R, Kiebish MA, Bountra C, Granger E, Narain NR. Ethnic Prevalence of Angiotensin-Converting Enzyme Deletion (D) Polymorphism and COVID-19 Risk: Rationale for Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers. *J Racial Ethn Health Disparities*. 2021;8(4):973-980. doi:10.1007/s40615-020-00853-0