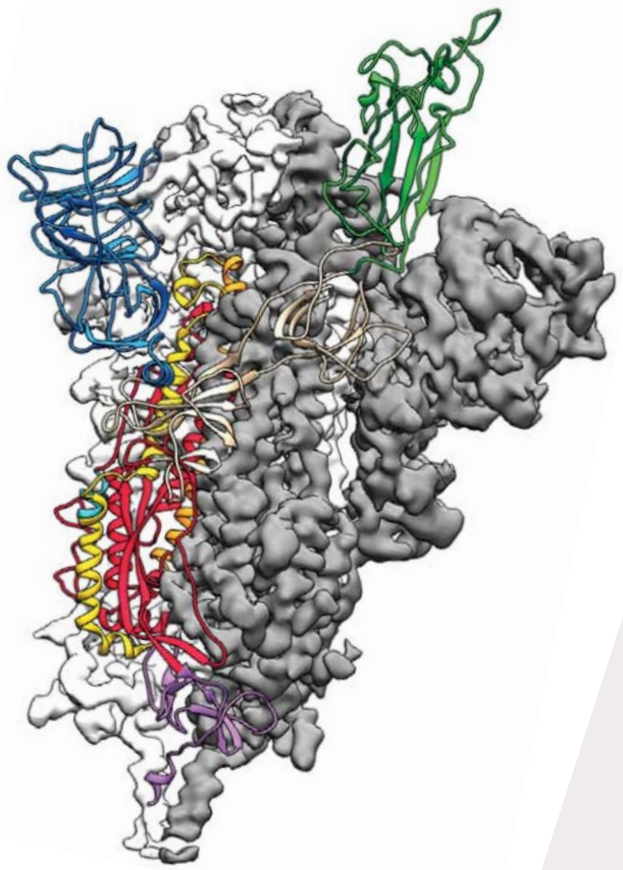


DAVID C. SOCOL, MD

32ND CLINICAL APPLICATIONS FOR AGE MANAGEMENT MEDICINE CONFERENCE

APRIL 8, 2022

The Genomics of a Pandemic: Human Polymorphisms, Viral Sabotage, and Functional Medicine Solutions

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

DISCLOSURES

- Dr. Socol has an Ownership Interest in Advanced Humeomics. All relevant commercial interests for this individual have been mitigated.

GOALS

01

Recognize genomic polymorphisms that contribute to the risk of viral infection.

02

Recognize proinflammatory genomic polymorphisms and understand their contribution to the viral immune response.

03

Manage viral infection using natural product pharmacopeia.

WHY?

AGENDA

Genomics

Polymorphisms

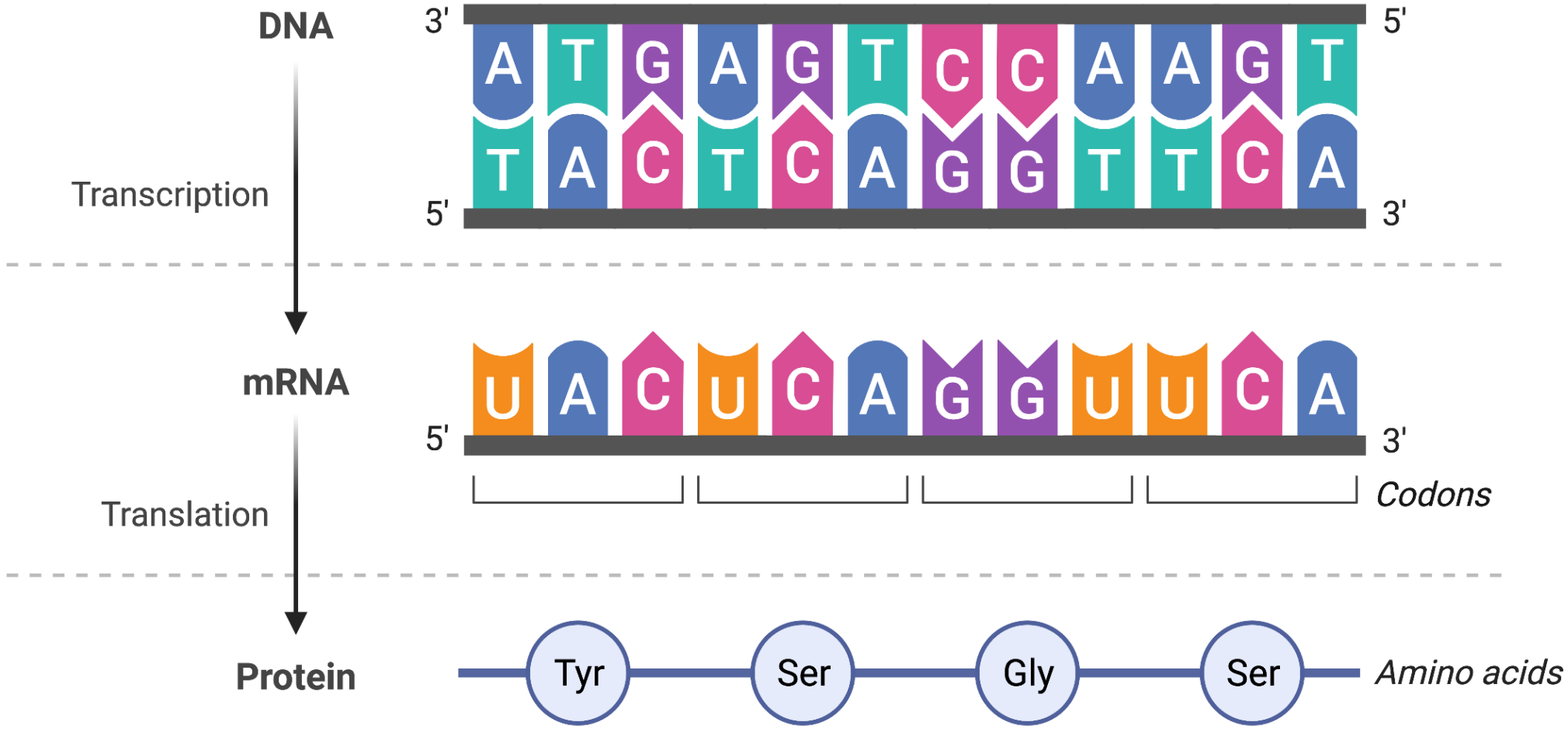
Viral engineering

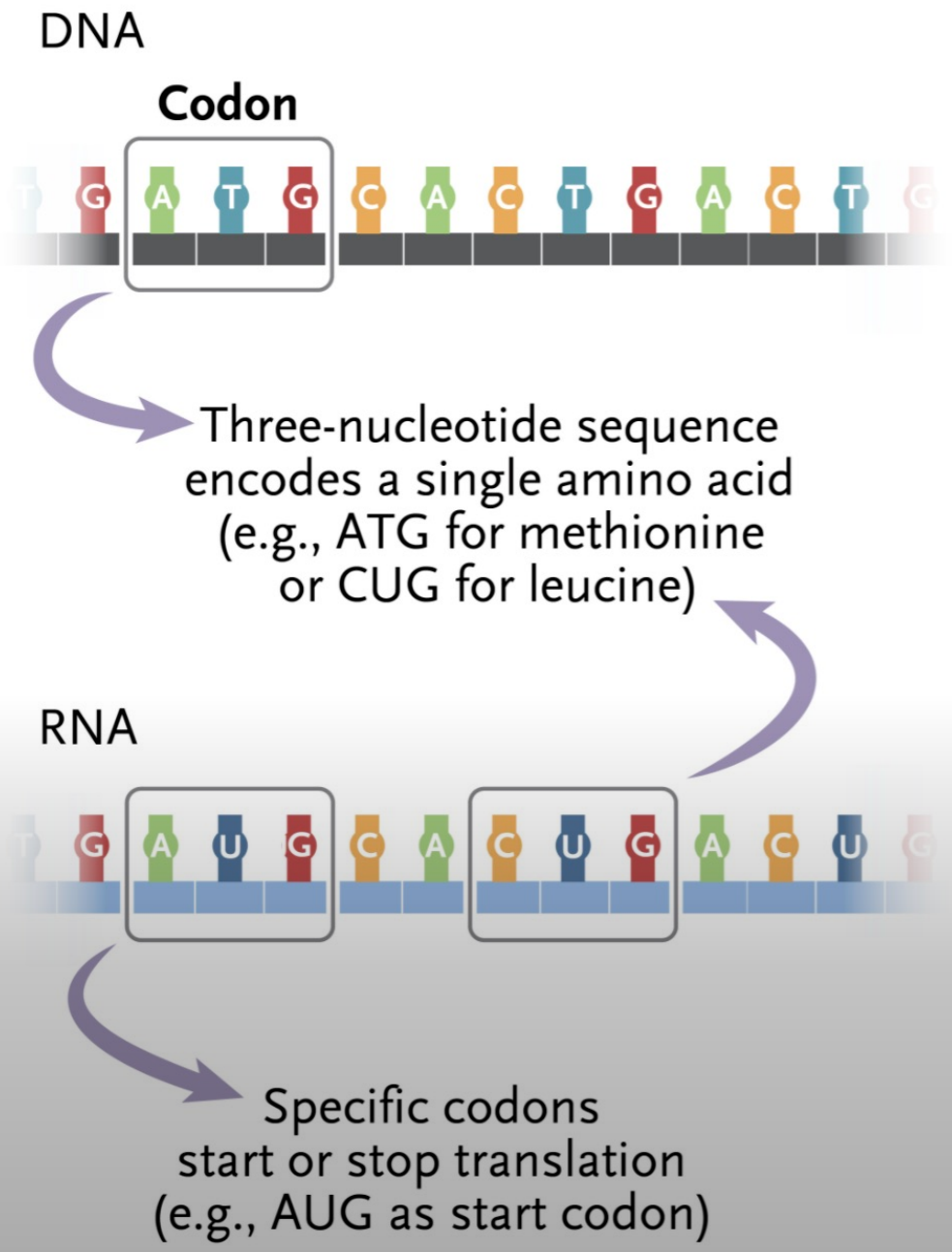
Solutions

REFRESHER -1

Chromosomes & Base Pairs

REFRESHER - 2



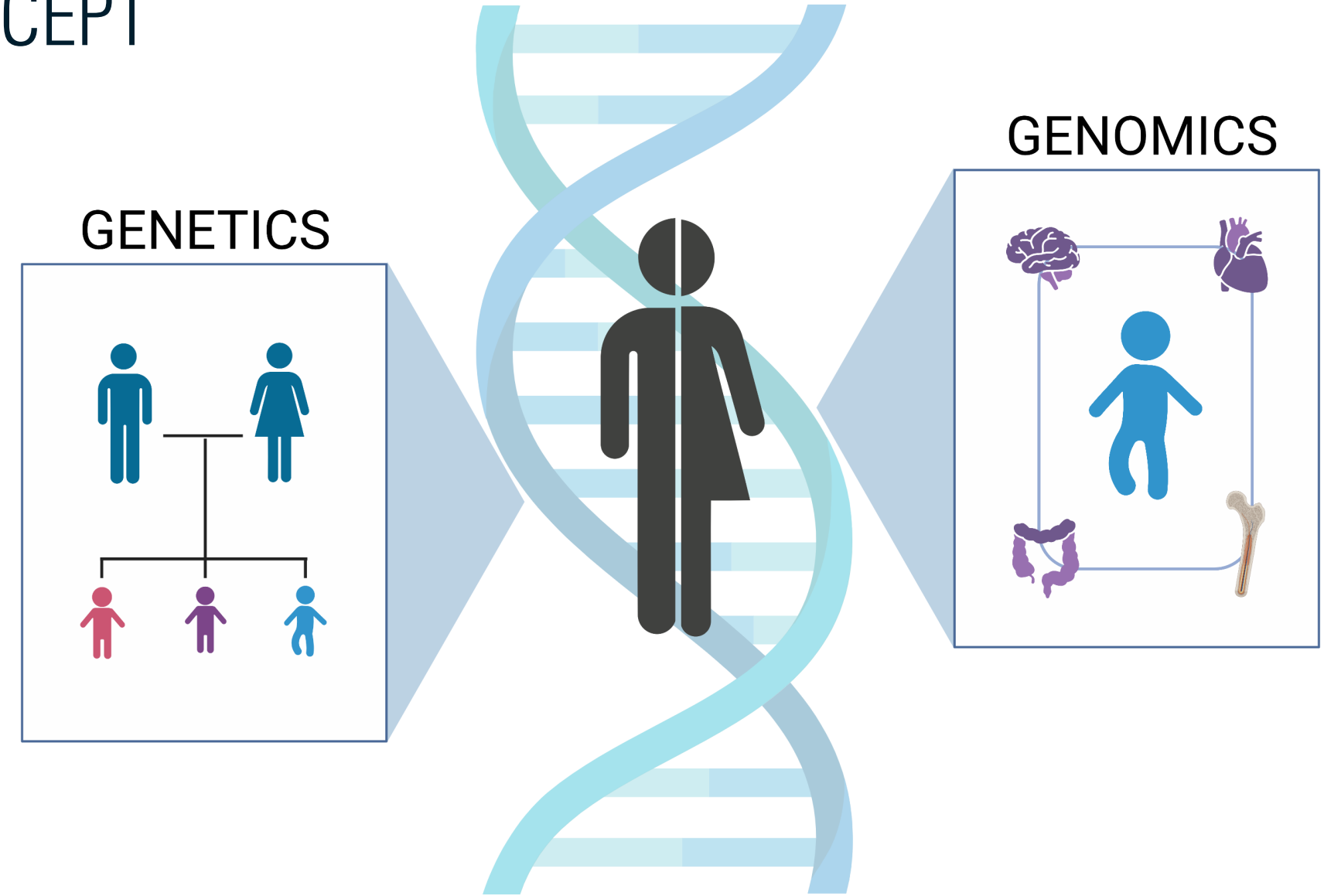


RNA codons

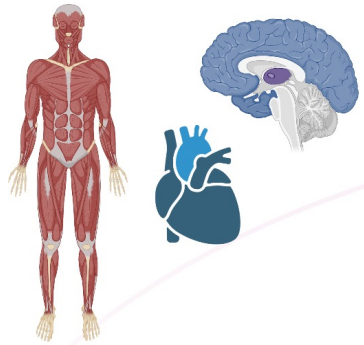
Amino Acids		Three-nucleotide sequence
Alanine	Ala (A)	GCA, GCC, GCG, GCU
Arginine	Arg (R)	AGA, AGG, CGA, CGC, CGG, CGU
Asparagine	Asn (N)	AAC, AAU
Aspartic acid	Asp (D)	GAC, GAU
Cysteine	Cys (C)	UGC, UGU
Glutamic acid	Glu (E)	GAA, GAG
Glutamine	Gln (Q)	CAA, CAG
Glycine	Gly (G)	GGA, GGC, GGG, GGU
Histidine	His (H)	CAC, CAU
Isoleucine	Ile (I)	AUA, AUC, AUU
Leucine	Leu (L)	UUA, UUG, CUA, CUC, CUG, CUU
Lysine	Lys (K)	AAA, AAG
Methionine	Met (M)	AUG
Phenylalanine	Phe (F)	UUC, UUU
Proline	Pro (P)	CCA, CCC, CCG, CCU
Serine	Ser (S)	AGC, AGU, UCA, UCC, UCG, UCU
Threonine	Thr (T)	ACA, ACC, ACG, ACU
Tryptophan	Trp (W)	UGG
Tyrosine	Tyr (Y)	UAC, UAU
Valine	Val (V)	GUA, GUC, GUG, GUU

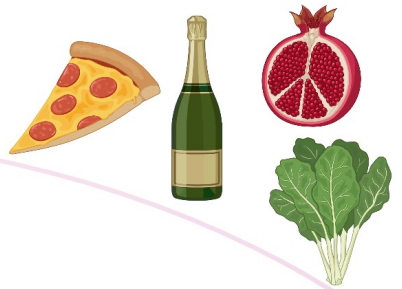
START codon: AUG **STOP codons: UAA, UAG, UGA**

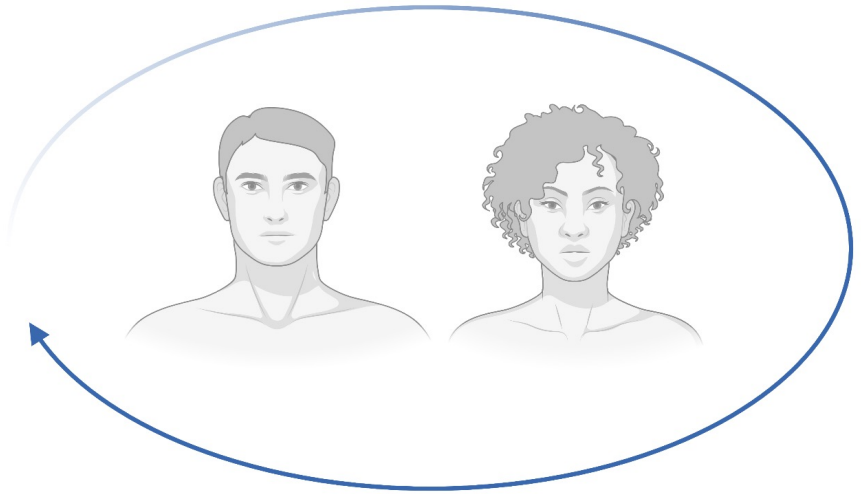
CONCEPT

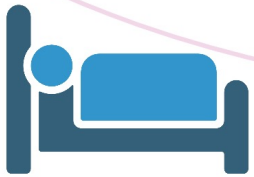


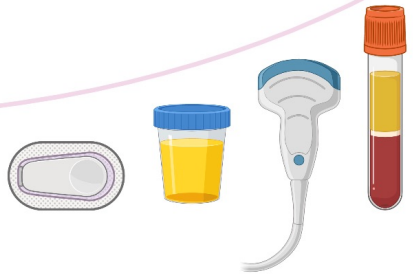
CLINICAL LIFECYCLE



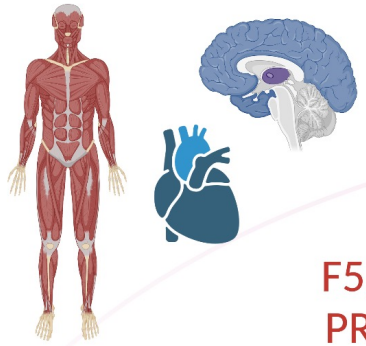




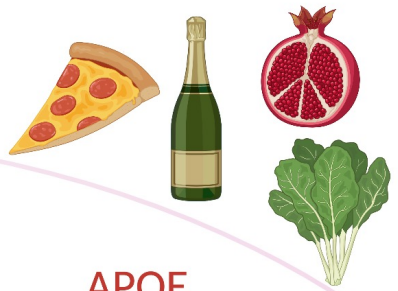




CLINICAL LIFECYCLE[2]



F5, F2
PROC
SERPIN1
NOS3

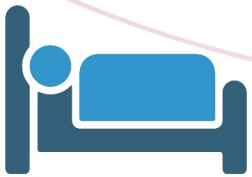


APOE
AOC1
HLA-DQ2.5
TCF7L2

ADRA1A
ADRB2
DIO2
CCL2
CNR2

BDNF
APOE
NTF3
PPARGC1A

NPSR1
CACNA1C
CYP1A2



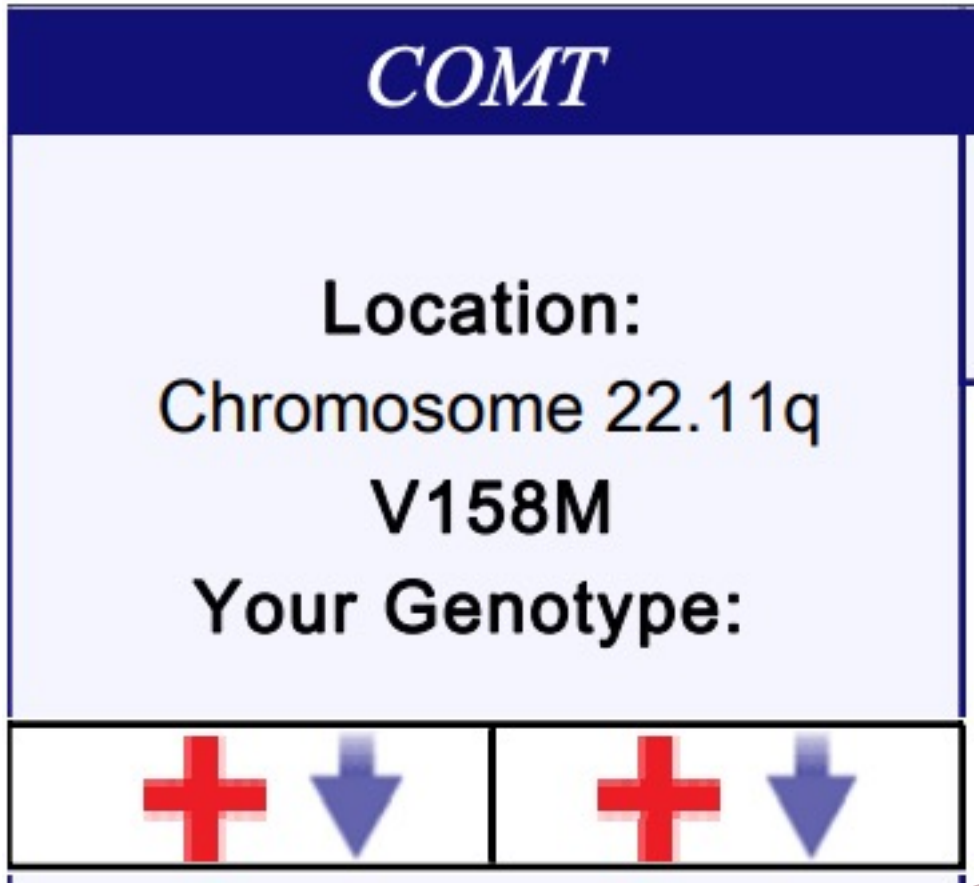
ENPP1
TCF7L2
KCNJ11
IGF-1

SINGLE NUCLEOTIDE POLYMORPHISMS (SNP)

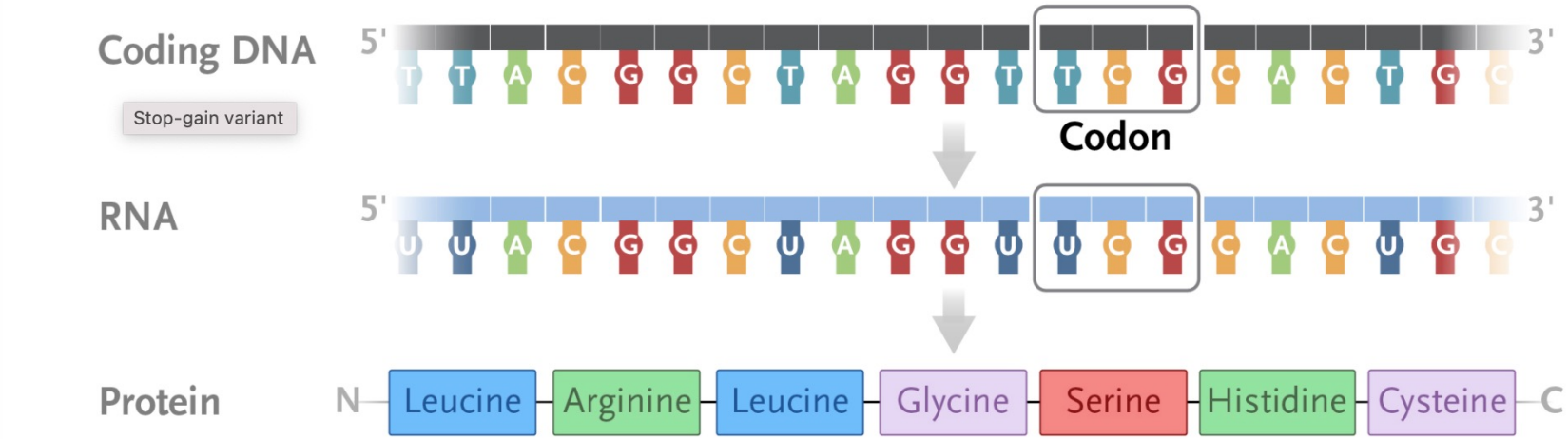
Increase in function
(promoter SNP)

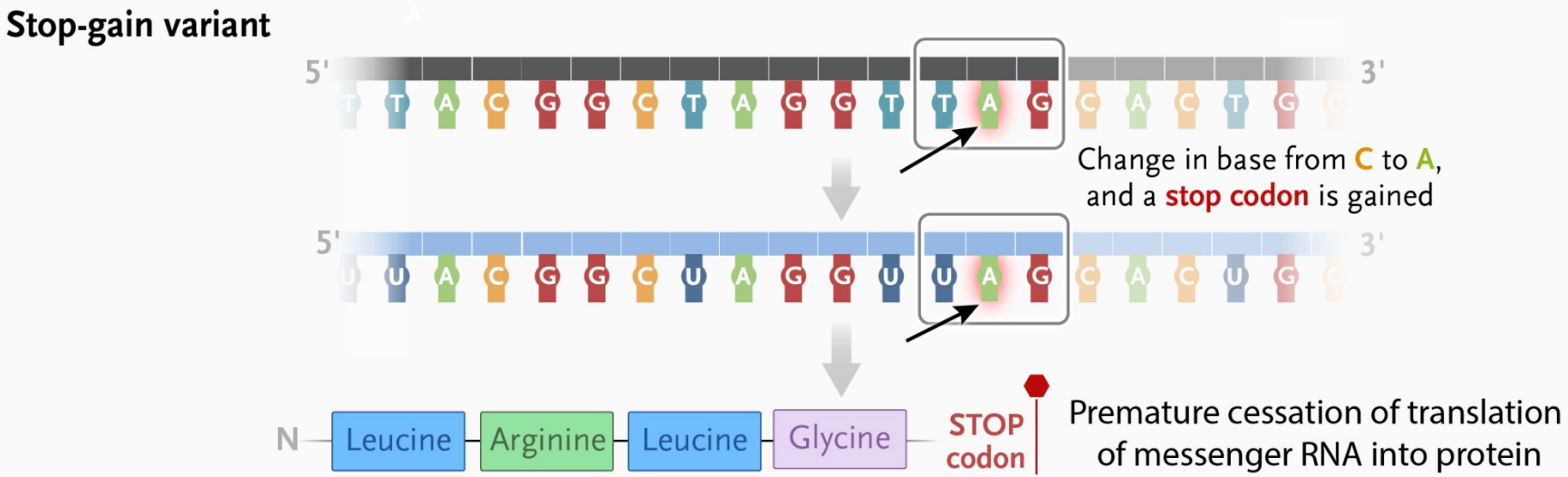
Decrease in function
(stop gain variant)

Loss of function

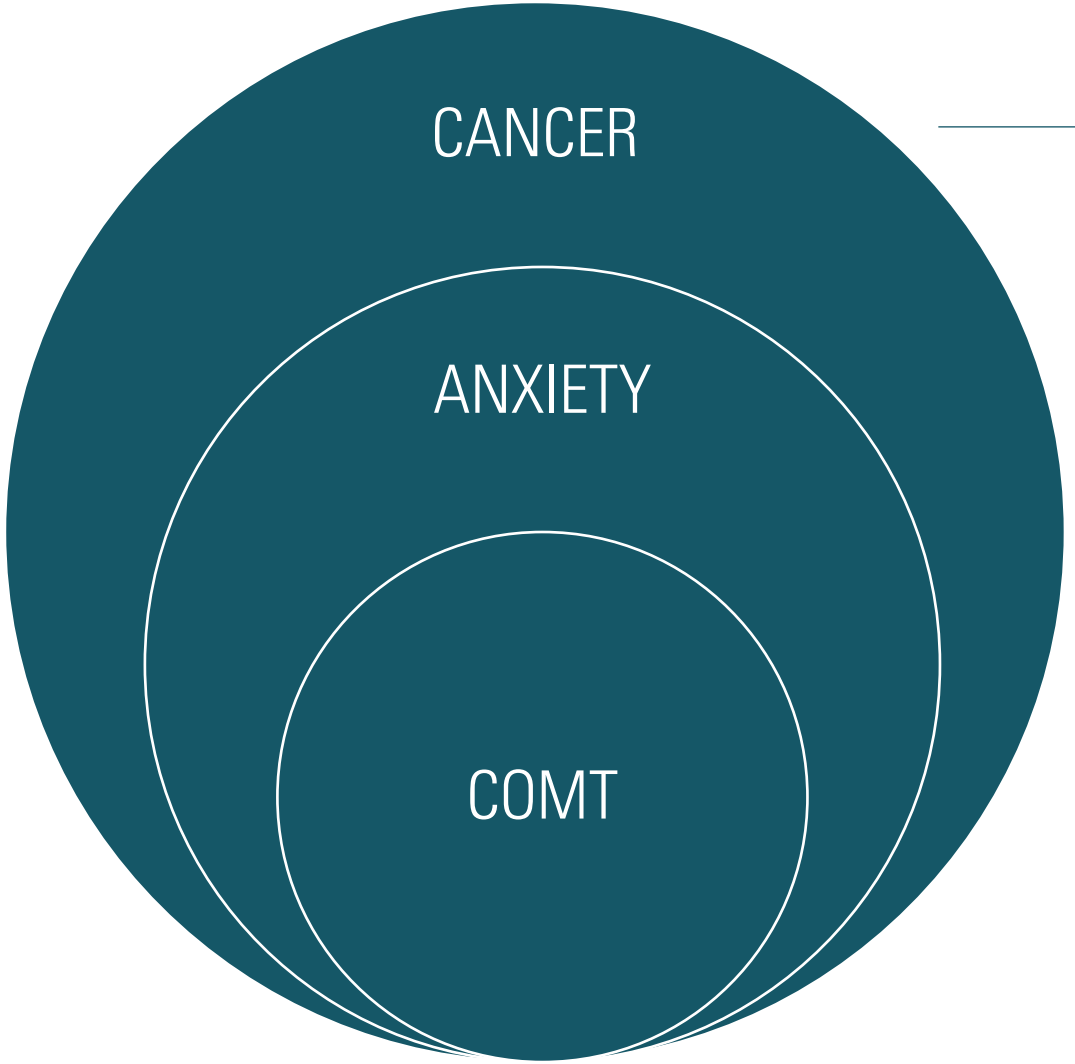


STOP GAIN VARIANT





INTEGRATIVE



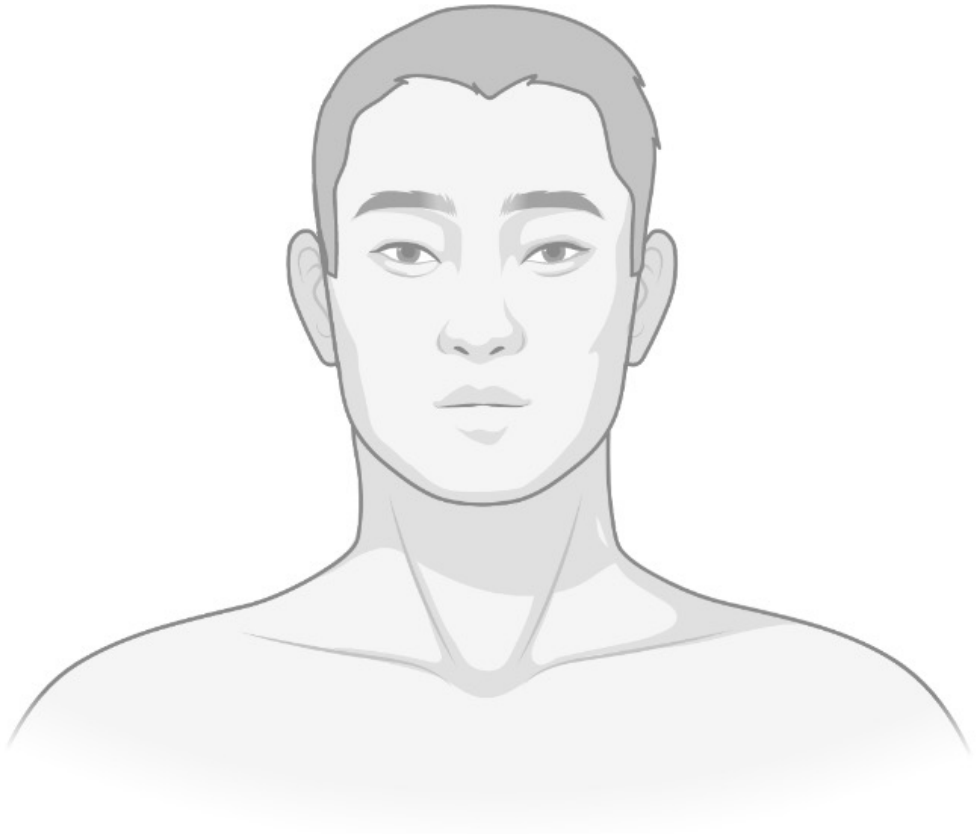
ESTROGEN METABOLISM

MENTAL HEALTH

CLINICAL EXPECTATIONS GENOMIC TOOLS

- Efficient
- Actionable
- Well calibrated
- Living Document

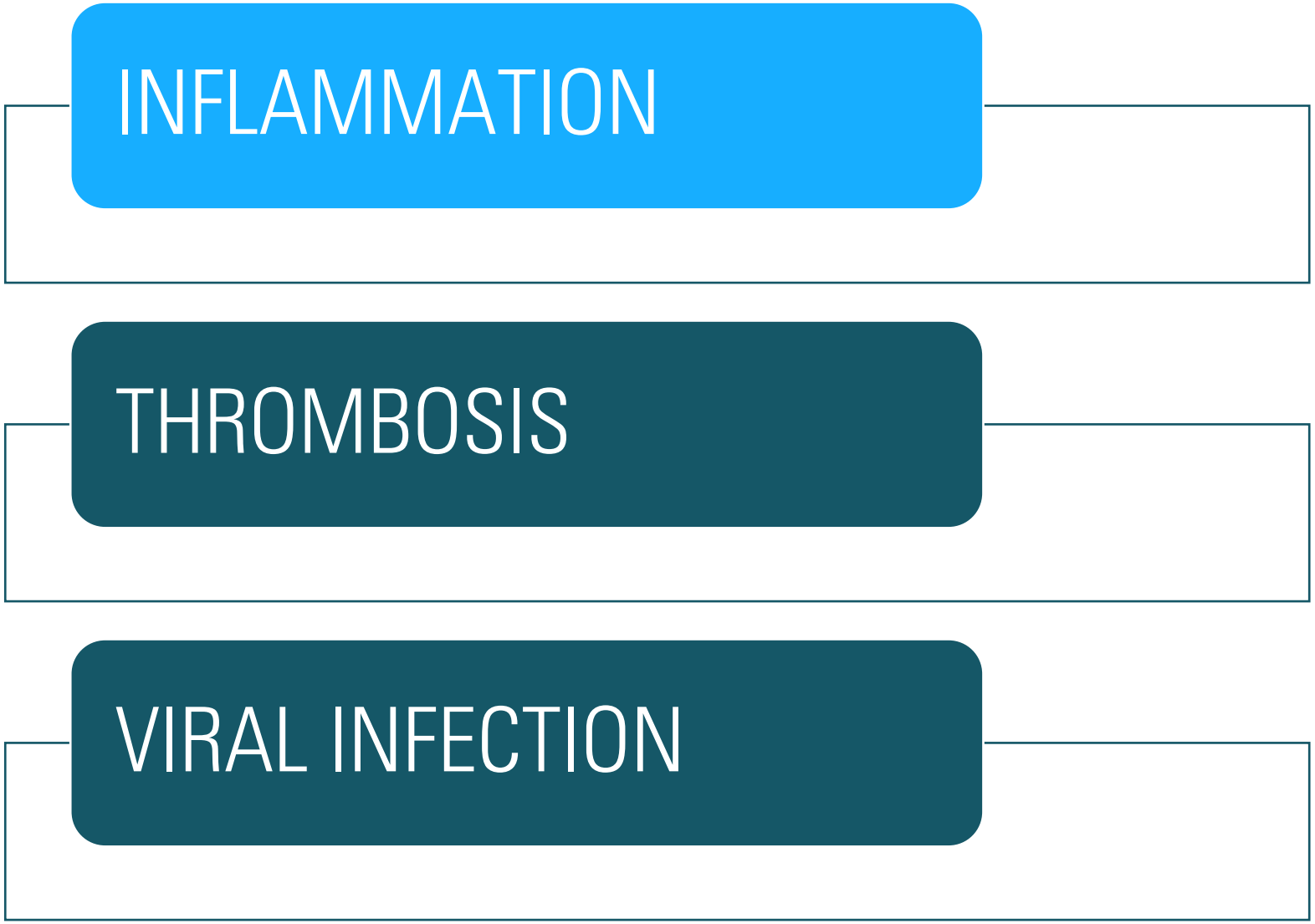
POLYMORPHISMS 



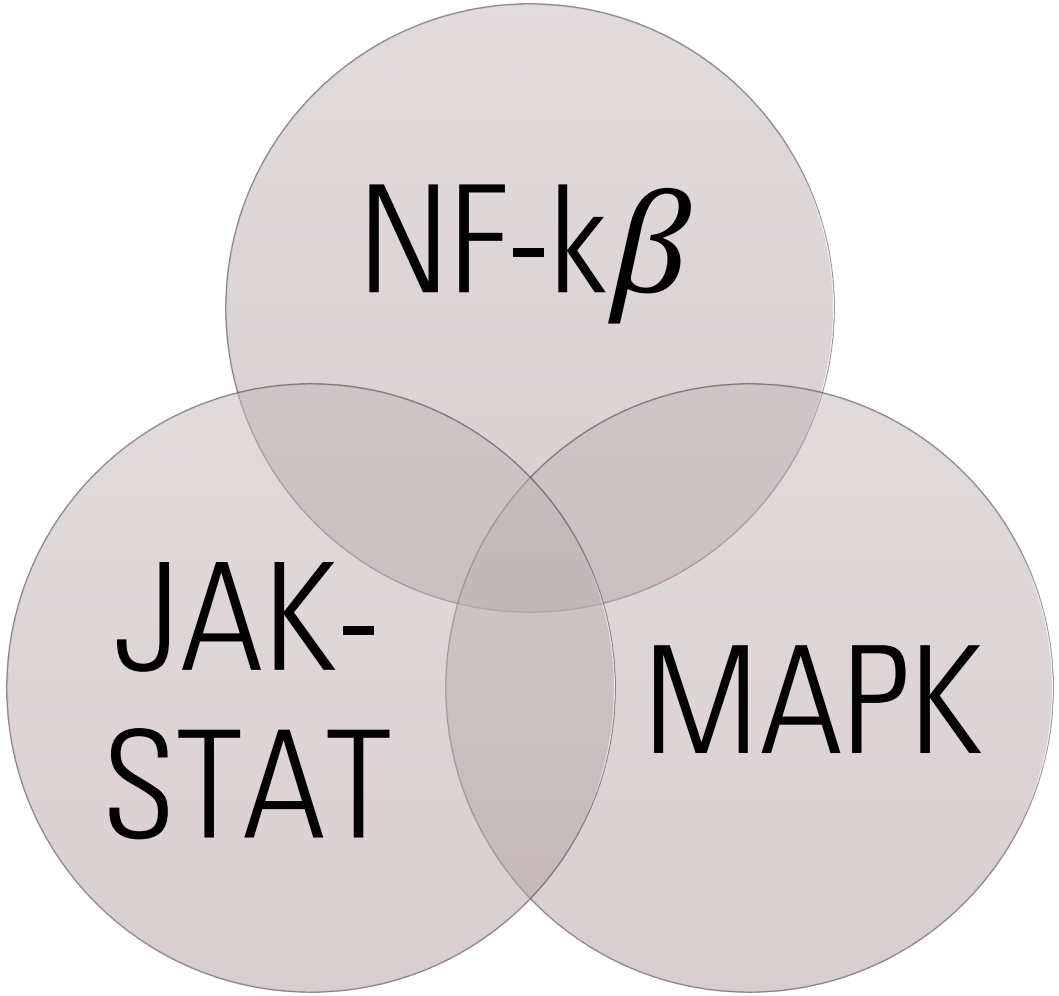
PATIENT X (PATIENT HISTORY)

- 48 y/o Caucasian
- TBF = 6.2%: ABF = 5.1%
- A1c = 5.4%
- Vitamin D = 32 mg/dL; Zn = 126 ng/dL
- TT= 962 ng/dL; FT= 172 ng/dL
- No autoimmune disease
- ApoE 3/3

GENOMIC PATHWAYS



INFLAMMATORY PATHWAYS



TUMOR NECROSIS FACTOR ALPHA

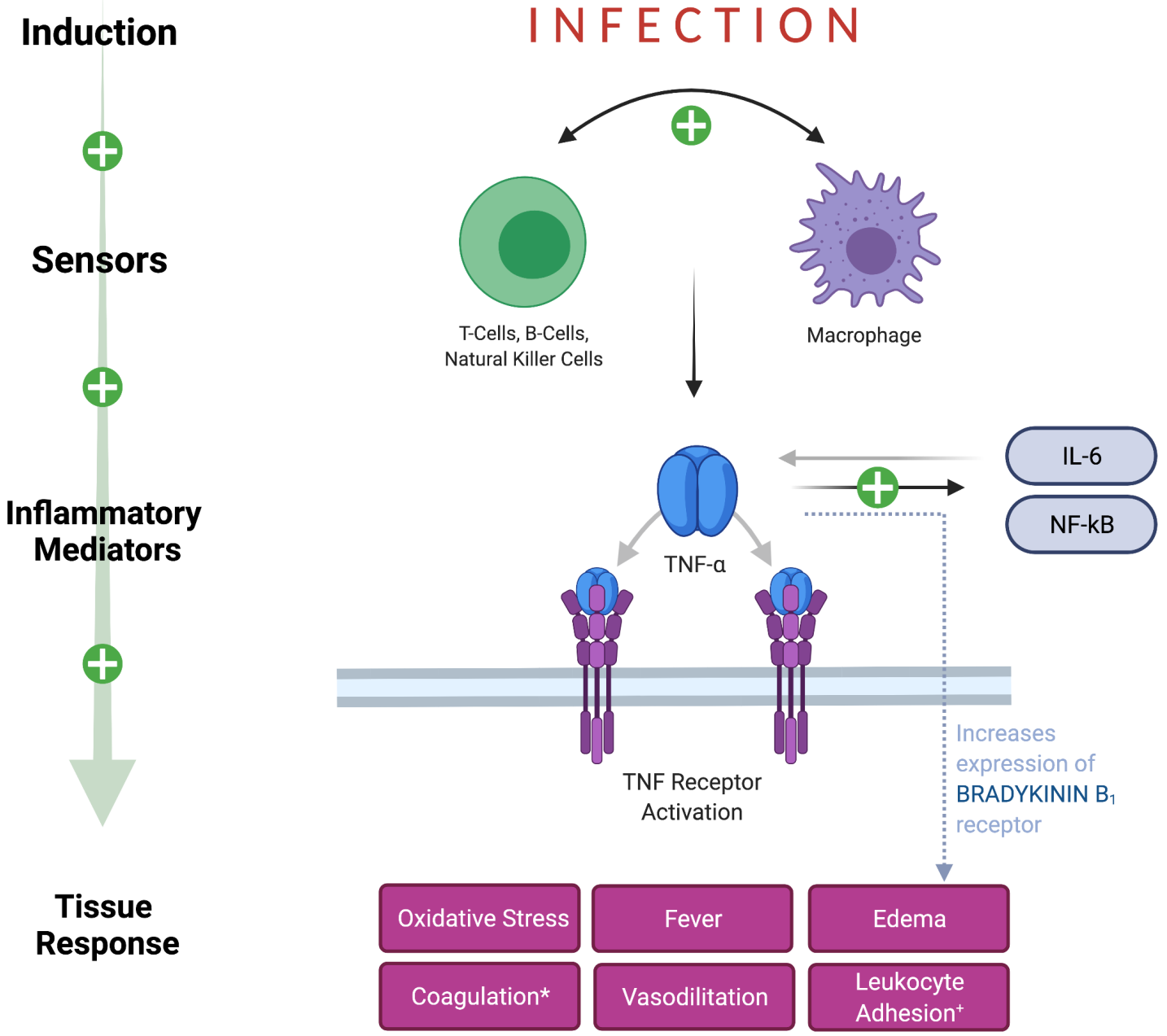
Risk SNP	Gene	Minor Allele	Patient Allele	Prevalence	Variant
rs1800629	TNF	A	AA	GG 2.6%	2

- 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.

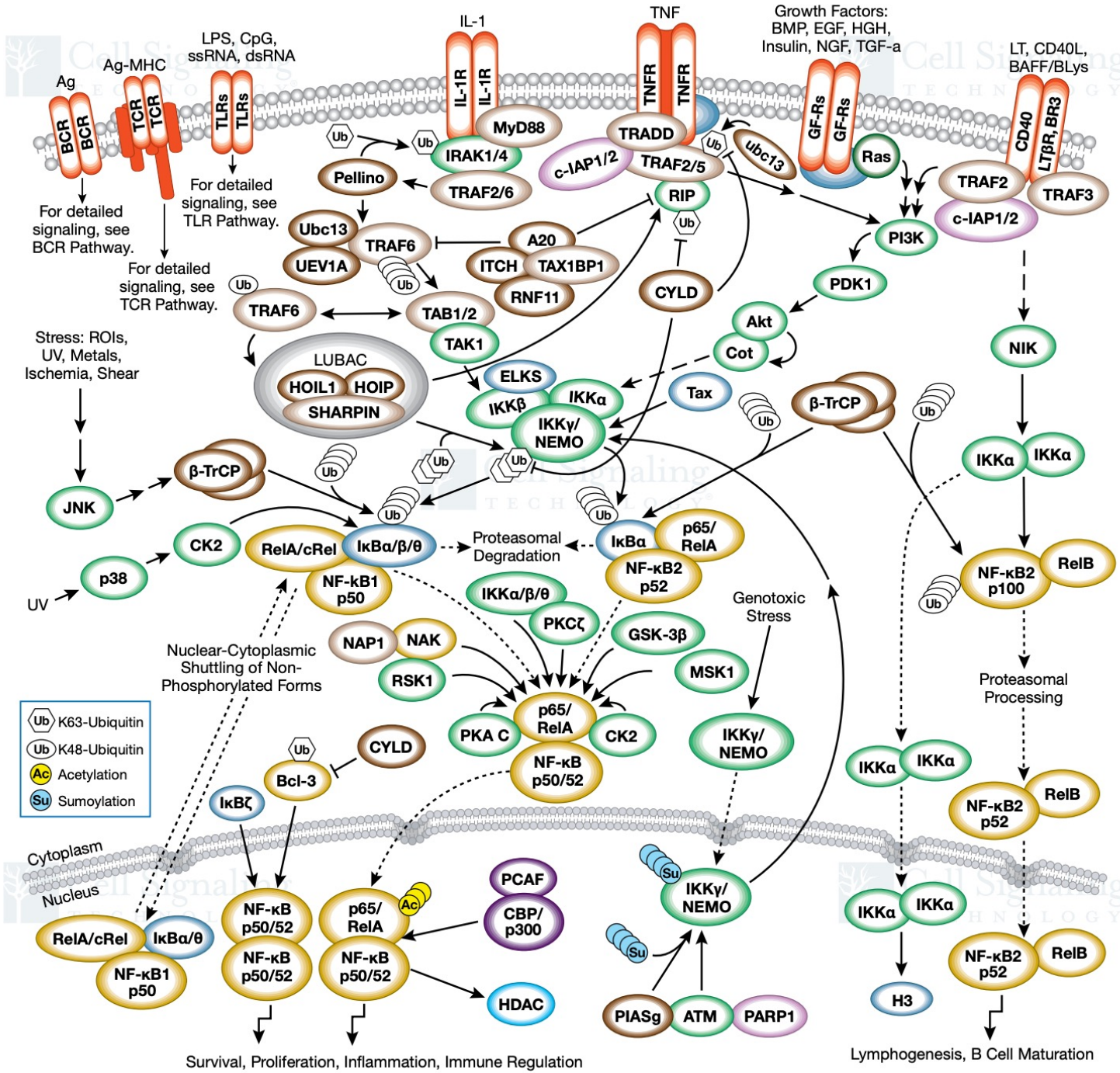
TNF-α

Risk SNPs:

- rs1800629
- rs361525
- rs1799724
- rs1799964

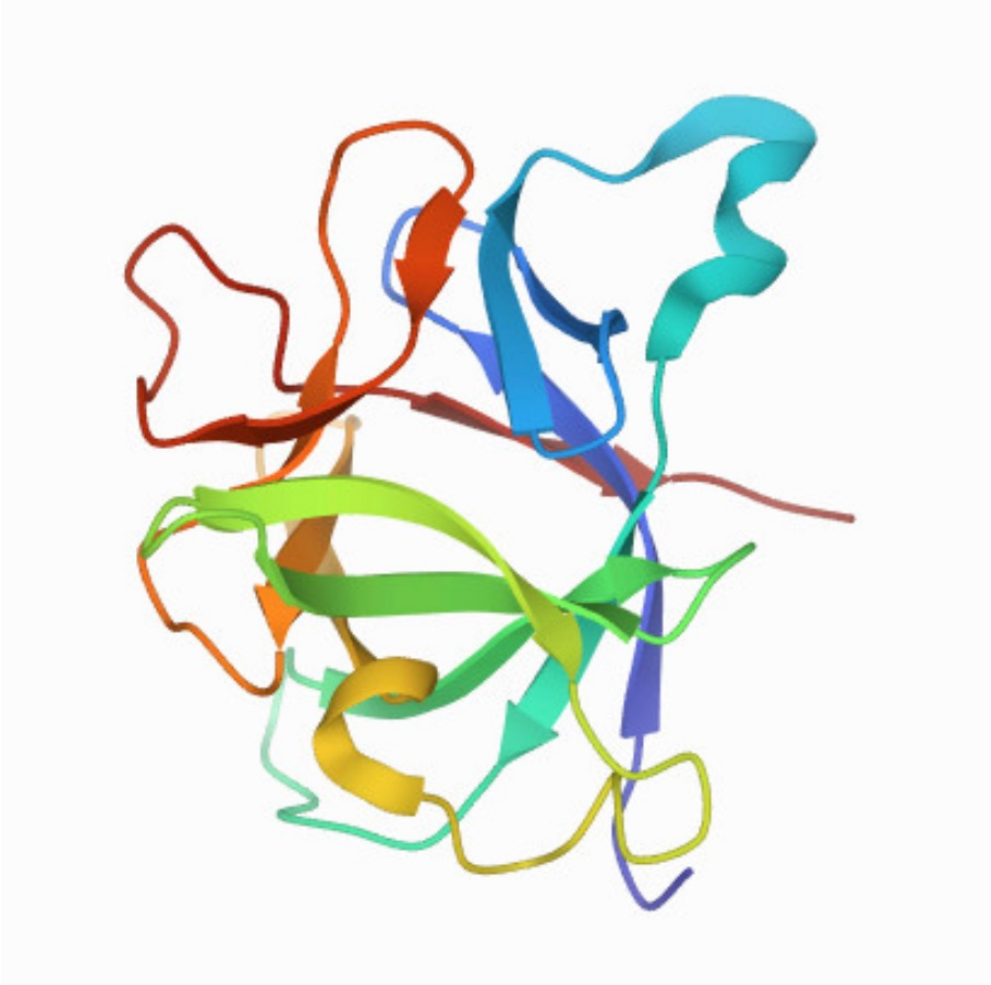


NF-Kβ PATHWAY



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

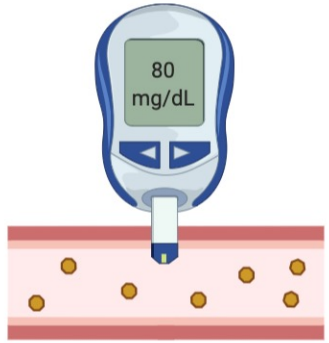


High-resolution three-dimensional structure of interleukin-1 beta in solution by three-and four-dimensional nuclear magnetic resonance spectroscopy. **PDB DOI:** 10.2210/pdb6I1B/pdb

IL6 - rs1800796

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

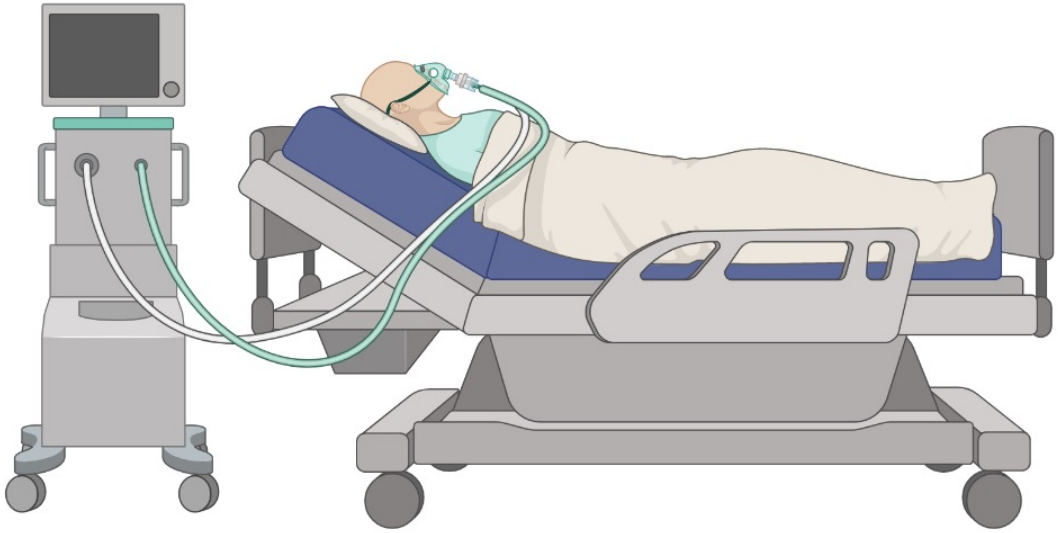
- SARS-CoV-2
  - Blood IL-6 level is highly correlated with the disease mortality and predicts the need for mechanical ventilation
  - SARS-CoV-2 induces release of IL6 that is independent of SNPs
  - IL-6 and TNF-α serum levels are known to be significant predictors of disease severity and death.



▲OR: ACUTE RESPIRATORY DISTRESS SYNDROME

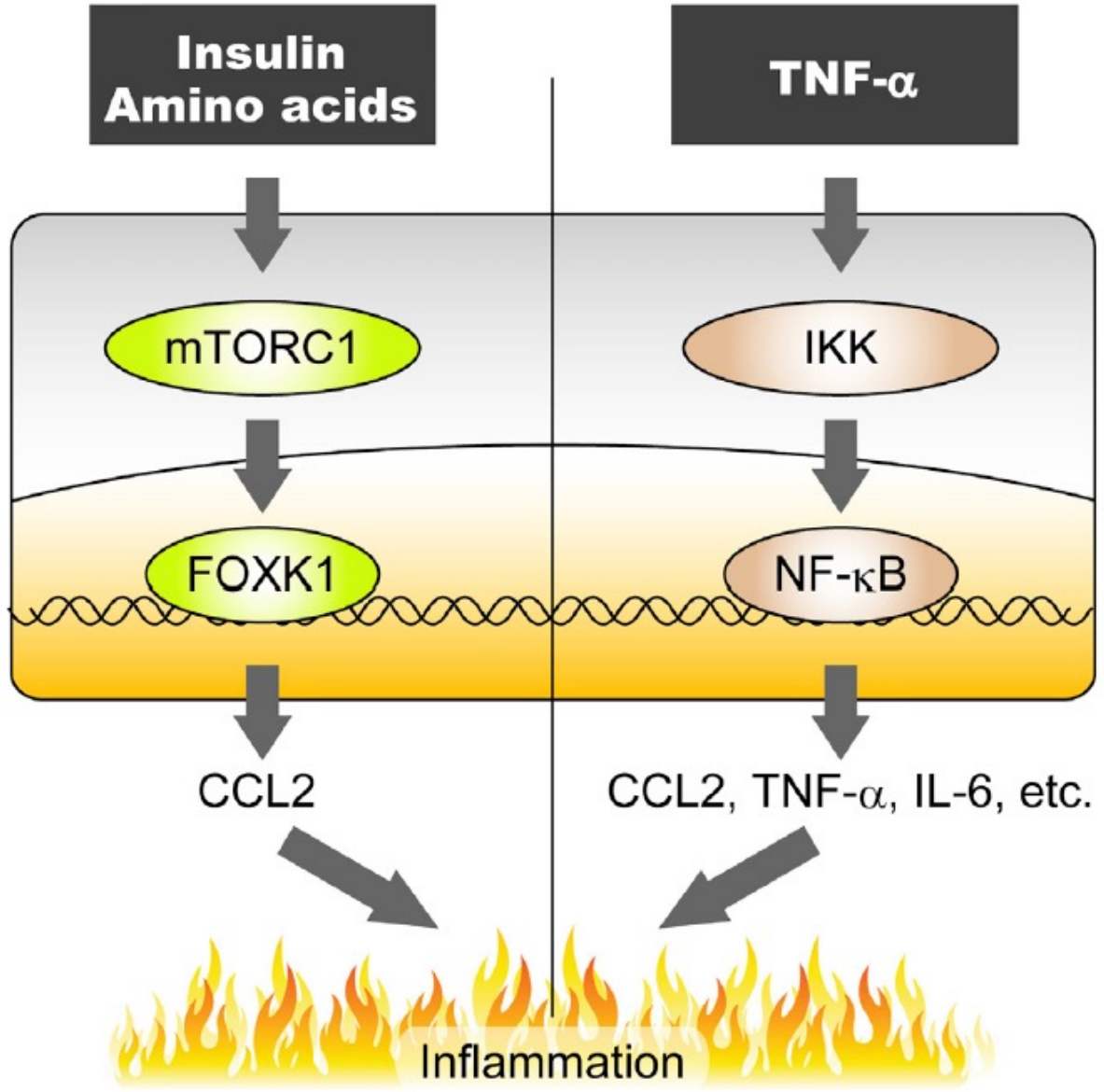
- MBL2 ▼
  - Baseline: Early warning system
  - Additive, w/ CCL2
  - OR = 2.88, heterozygous SNP

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



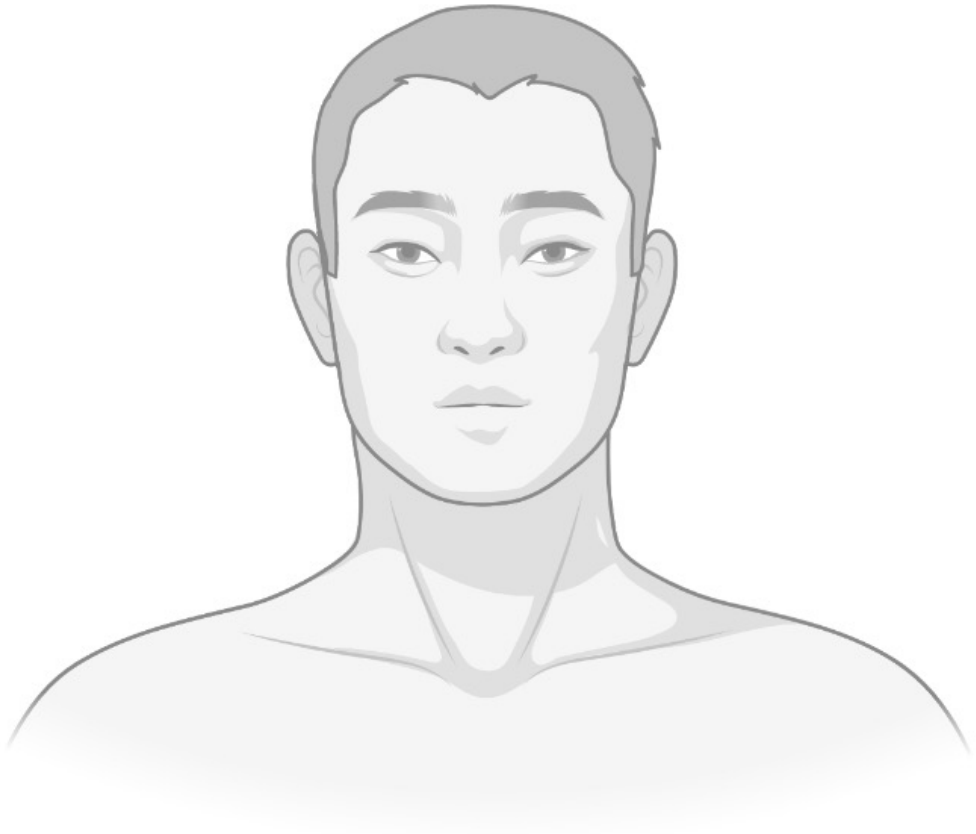
NONCANONICAL PATHWAY FOR REGULATION OF CCL2

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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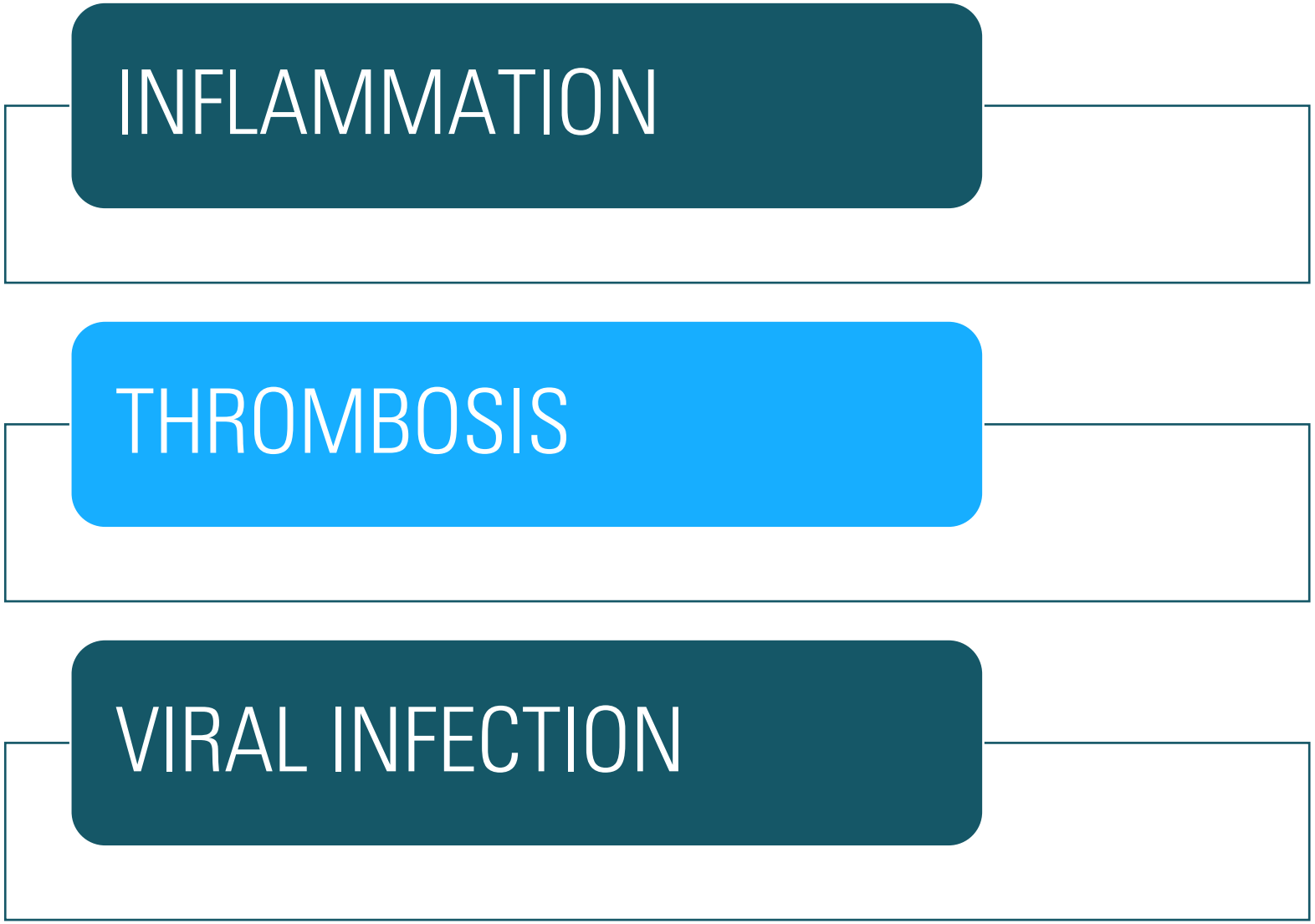
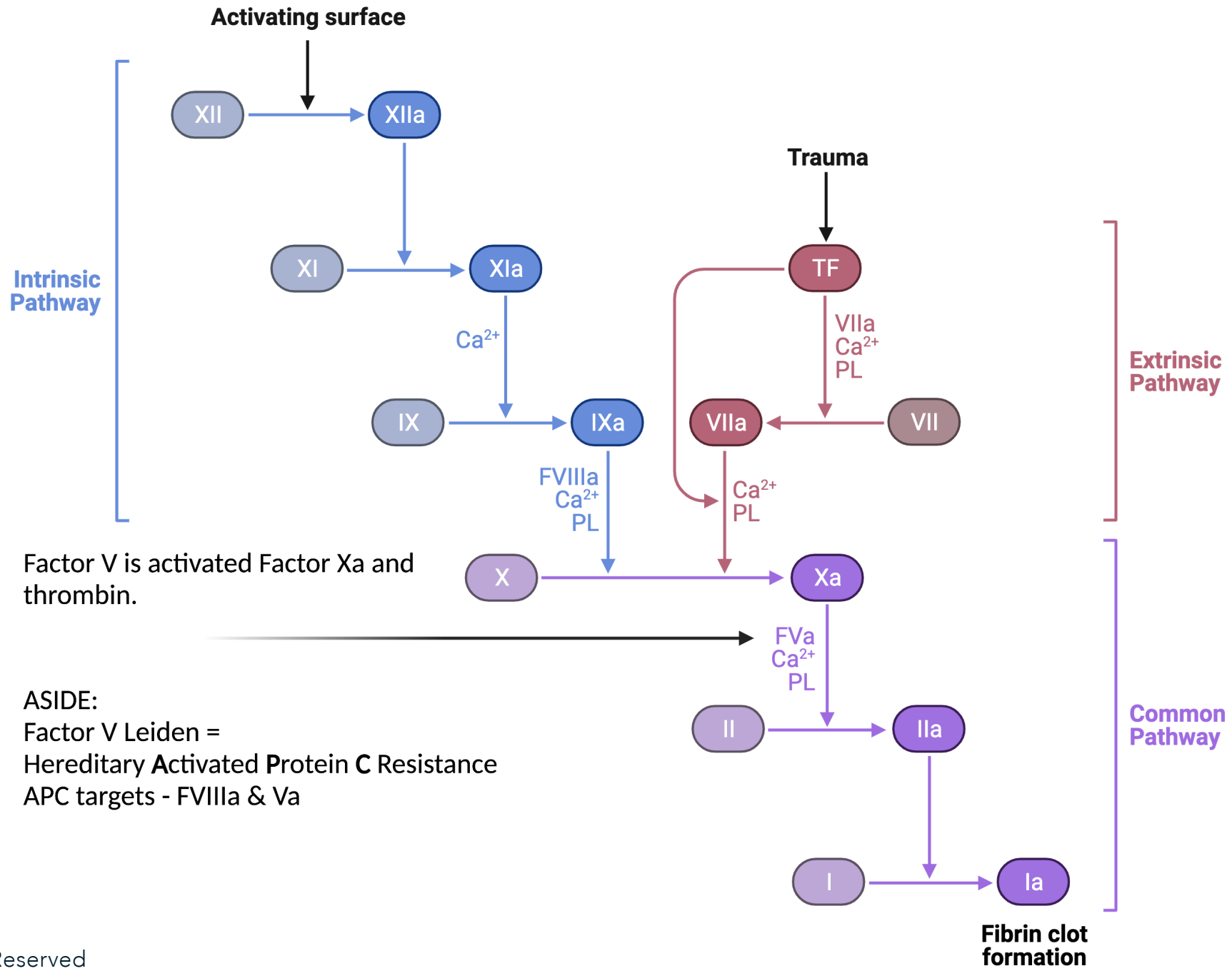
- Inflammatory SNPs
  - NLRP3, CARD8, CCL2 & TNF-a
  - IL-1B

GENOMIC PATHWAYS





Factor V is activated Factor Xa and thrombin.

ASIDE:
Factor V Leiden =
Hereditary **A**ctivated **P**rotein **C** Resistance
APC targets - FVIIIa & Va

HYPERCOAGULABLE

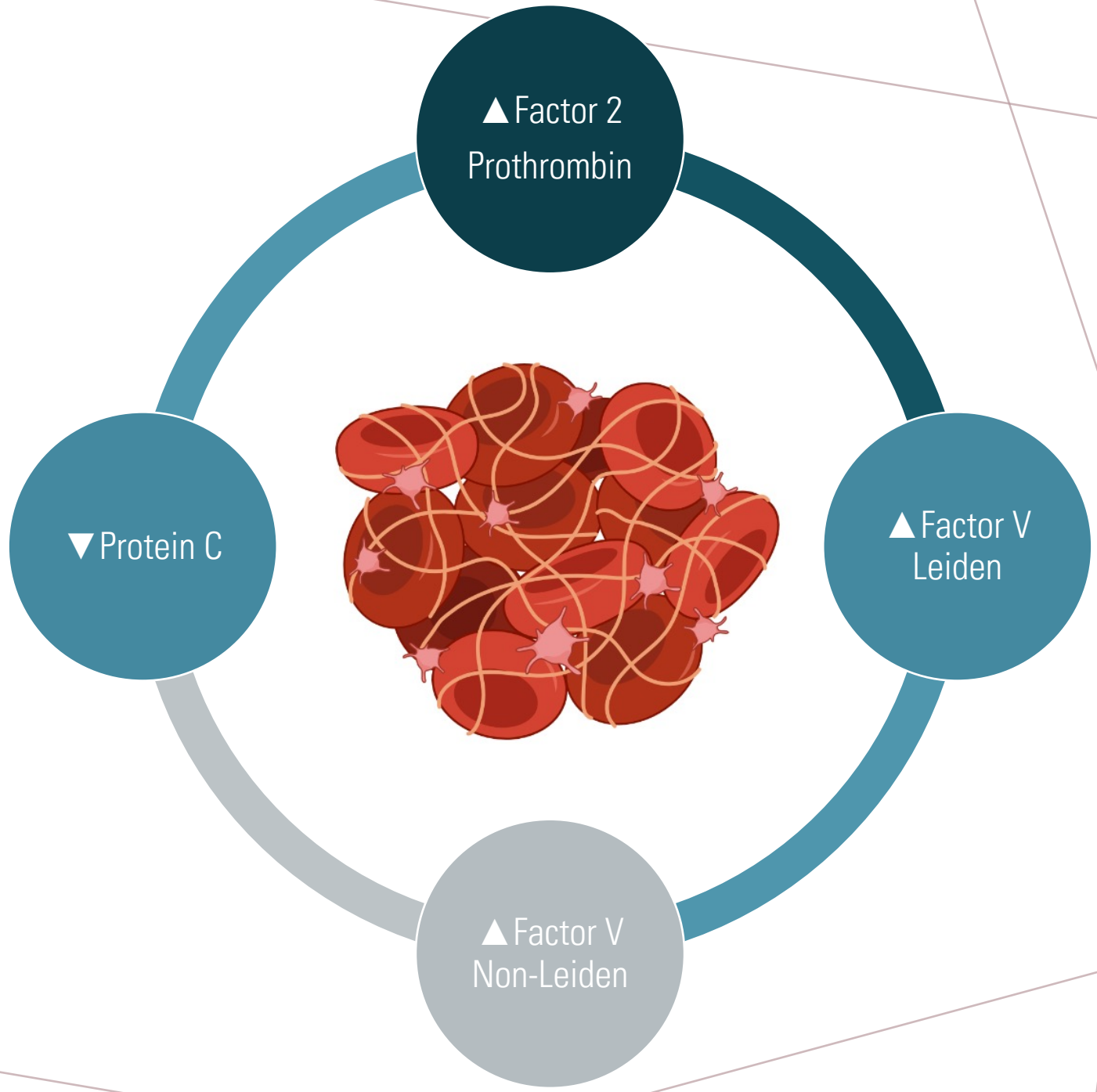
OR:

F2: 5.5, central venous thrombosis

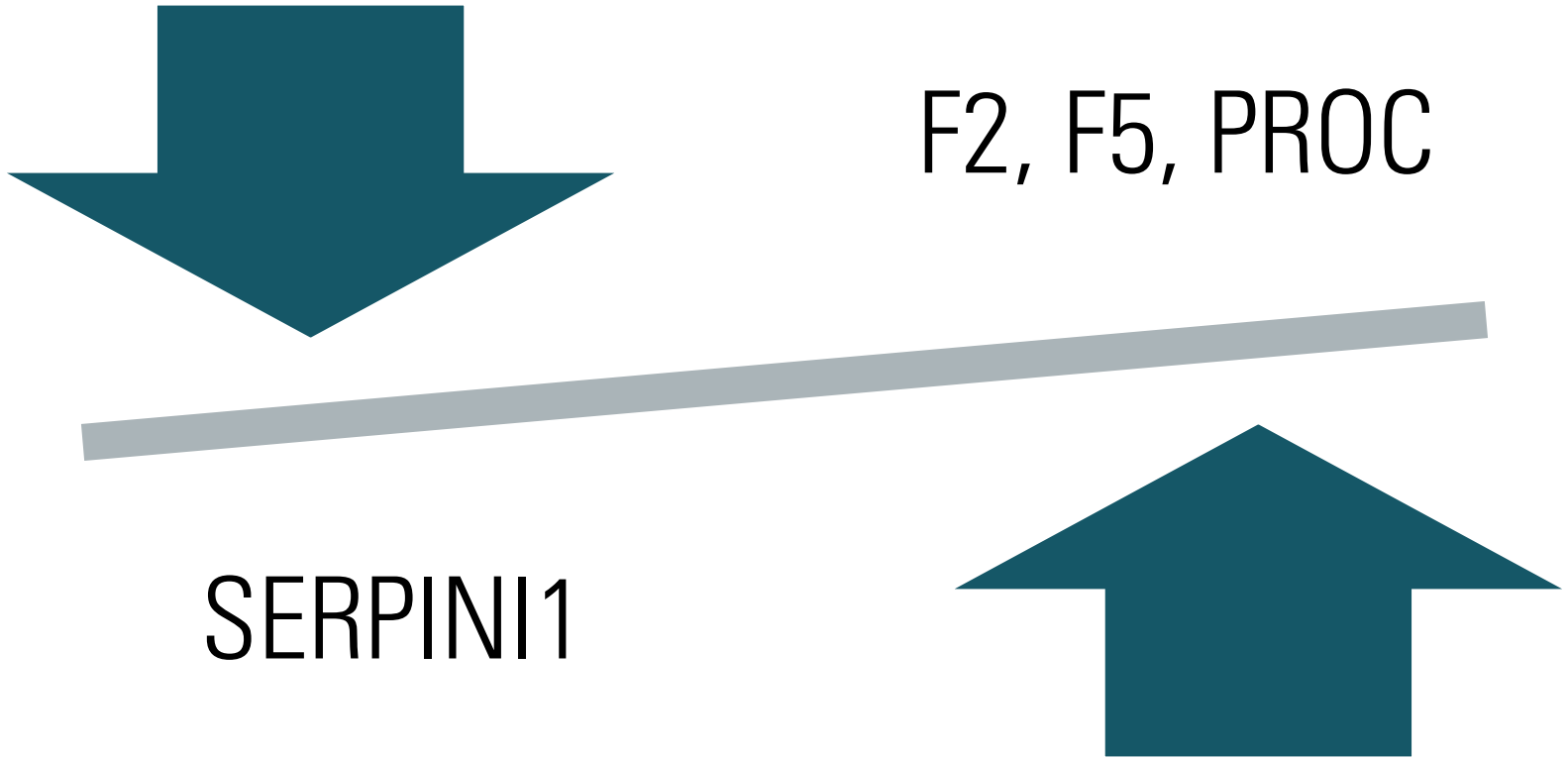
F5 Leiden: 50x (homozygous, lifetime)

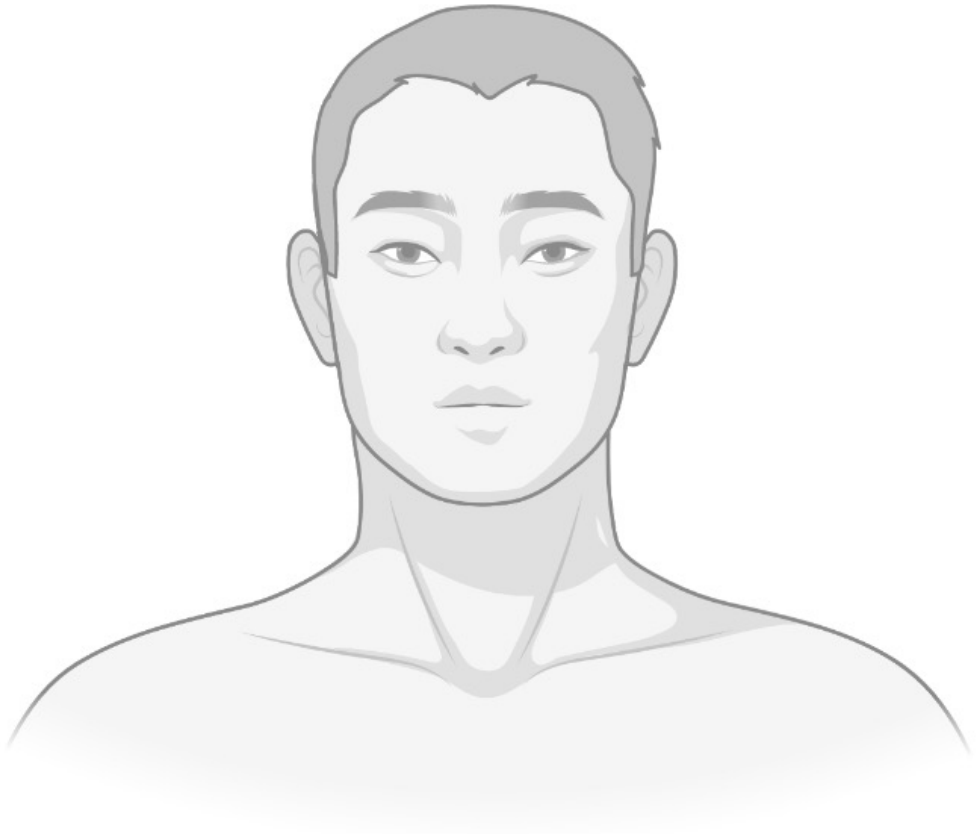
F5 – Non-Leiden: increased risk of CHD (OR = 2.63) and stroke (OR = 13.51) in women

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



COUNTERBALANCE





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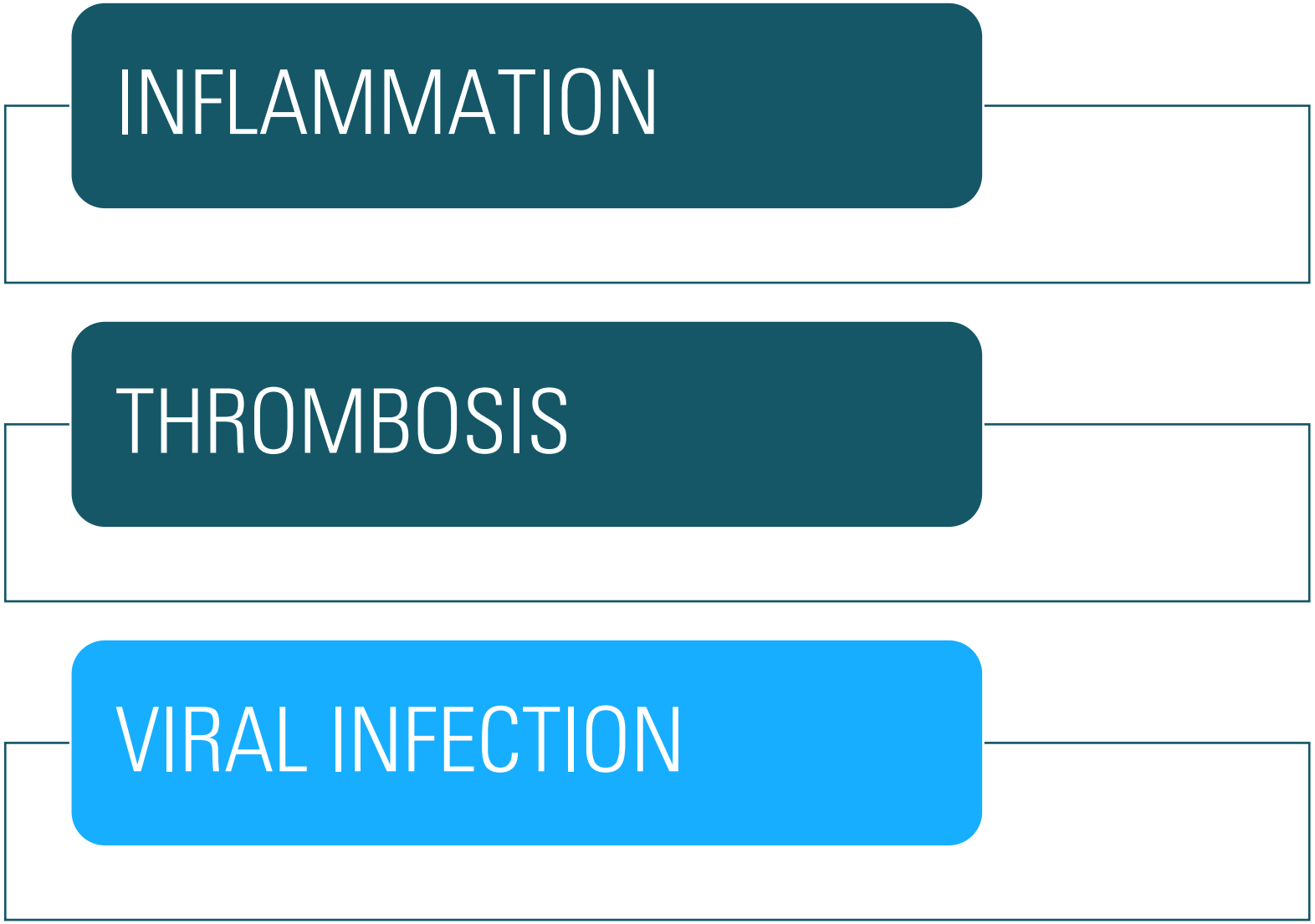
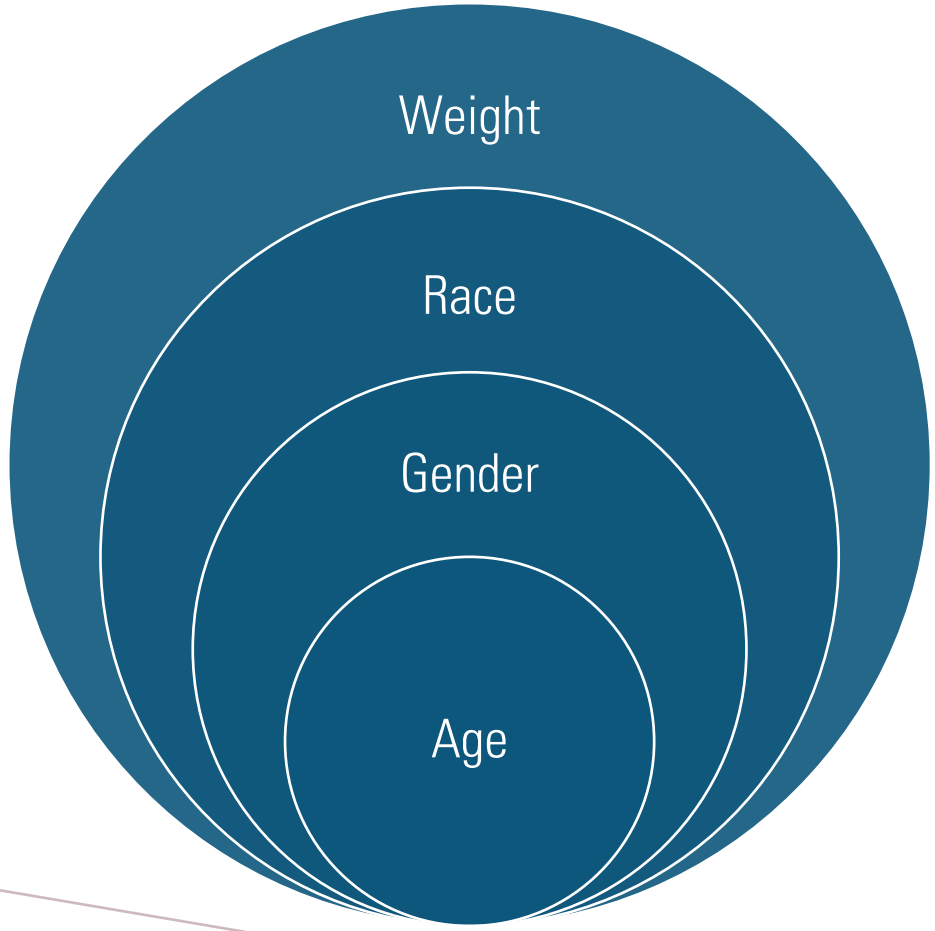
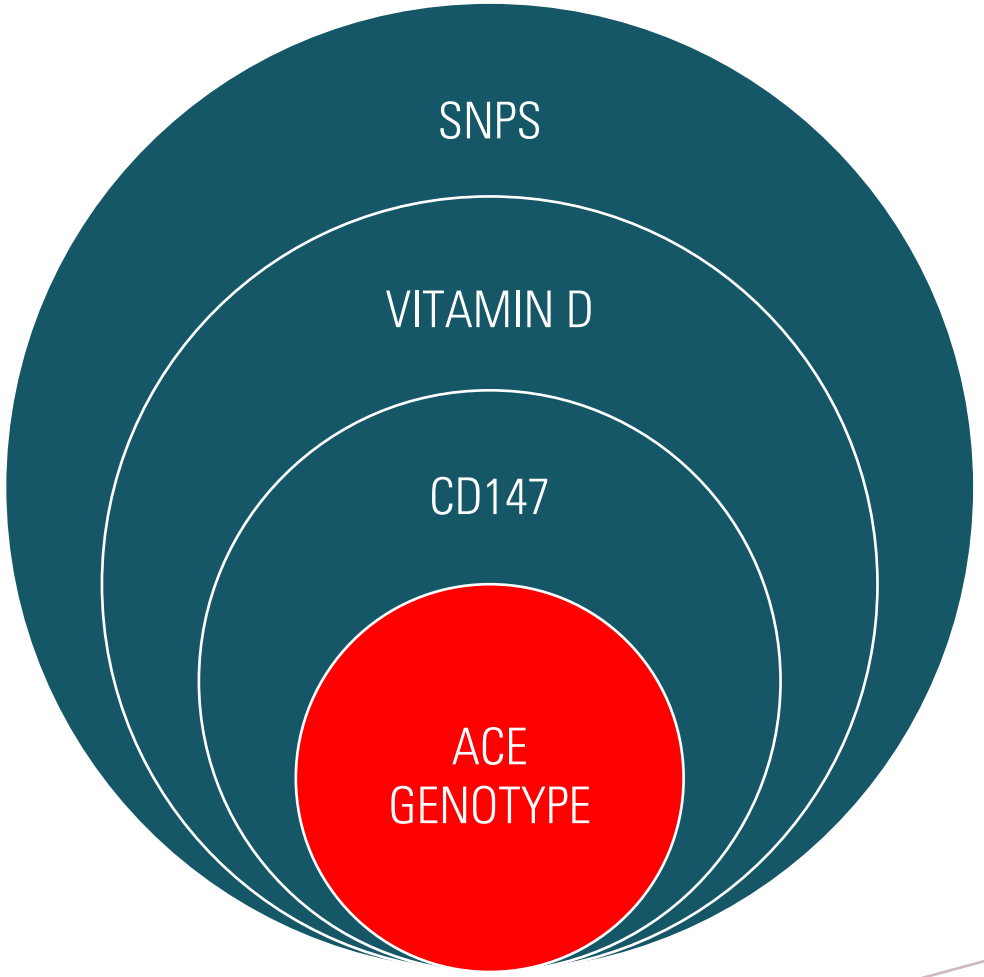
- Inflammatory SNPs
  - NLRP3, CARD8, CCL2 & TNF-a
  - IL-1B
- Hypercoagulability
  - Factor V Non-Leiden
  - Protein C

GENOMIC PATHWAYS



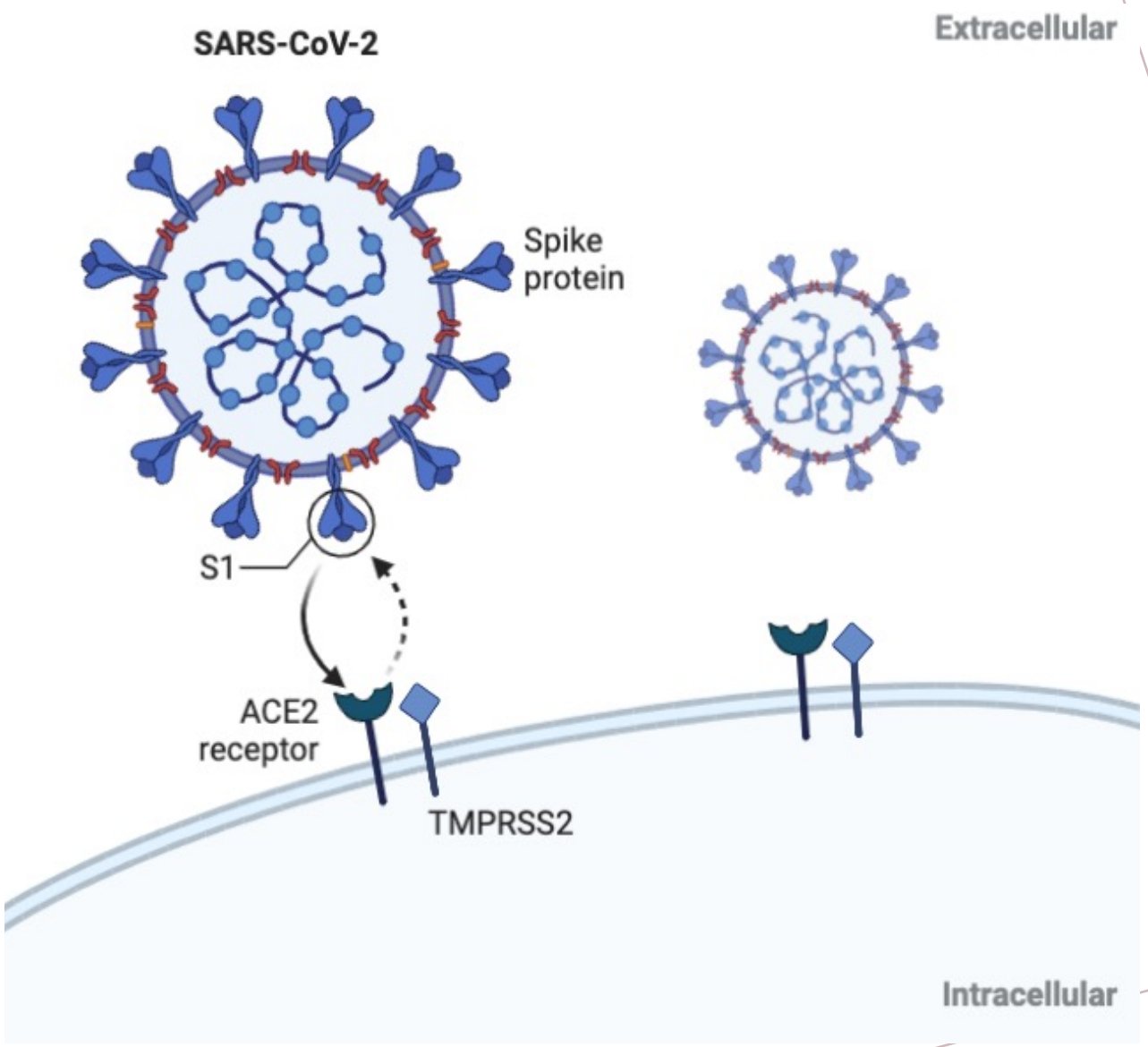
FROM COVID PHENOTYPE TO ACE GENOTYPE





ACE2 RECEPTOR

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



ACE1 GENOTYPE, CHROMOSOME 17

- ACE DD vs. ACE II (vs. DI)

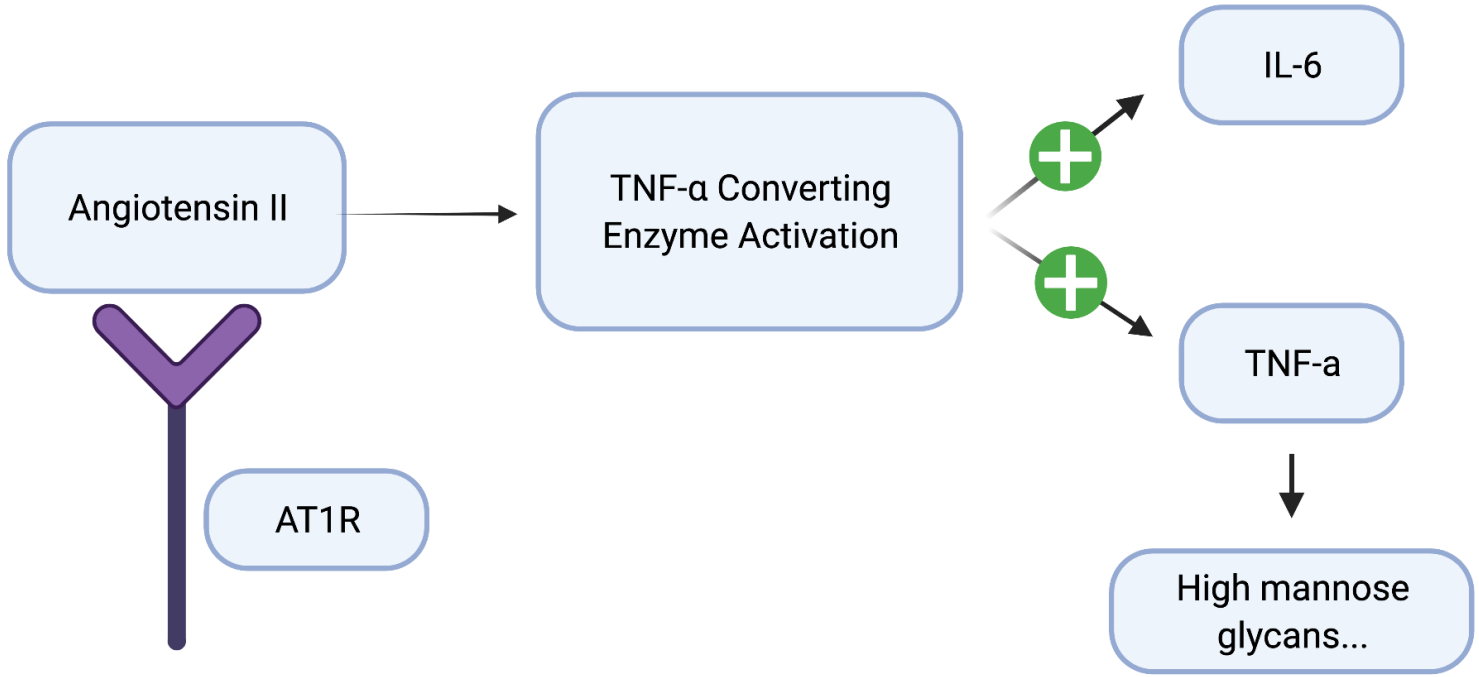
- ↑ 70% angiotensin converting enzyme (ACE) →
  - (+) enhanced endothelial tight junctions
  - (+) LDL oxidation
  - associated with a higher plasma level of ACE and an increased risk of CAD, myocardial infarction and cardiomyopathies
  - (+) Hypertension.

- SARS-CoV2
  - Reduction in ACE2 (due to overactivation of RAS), increase ACE/ACE2 , increase in angiotensin II.

SARS-COV2, TNF-α & IL-6

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

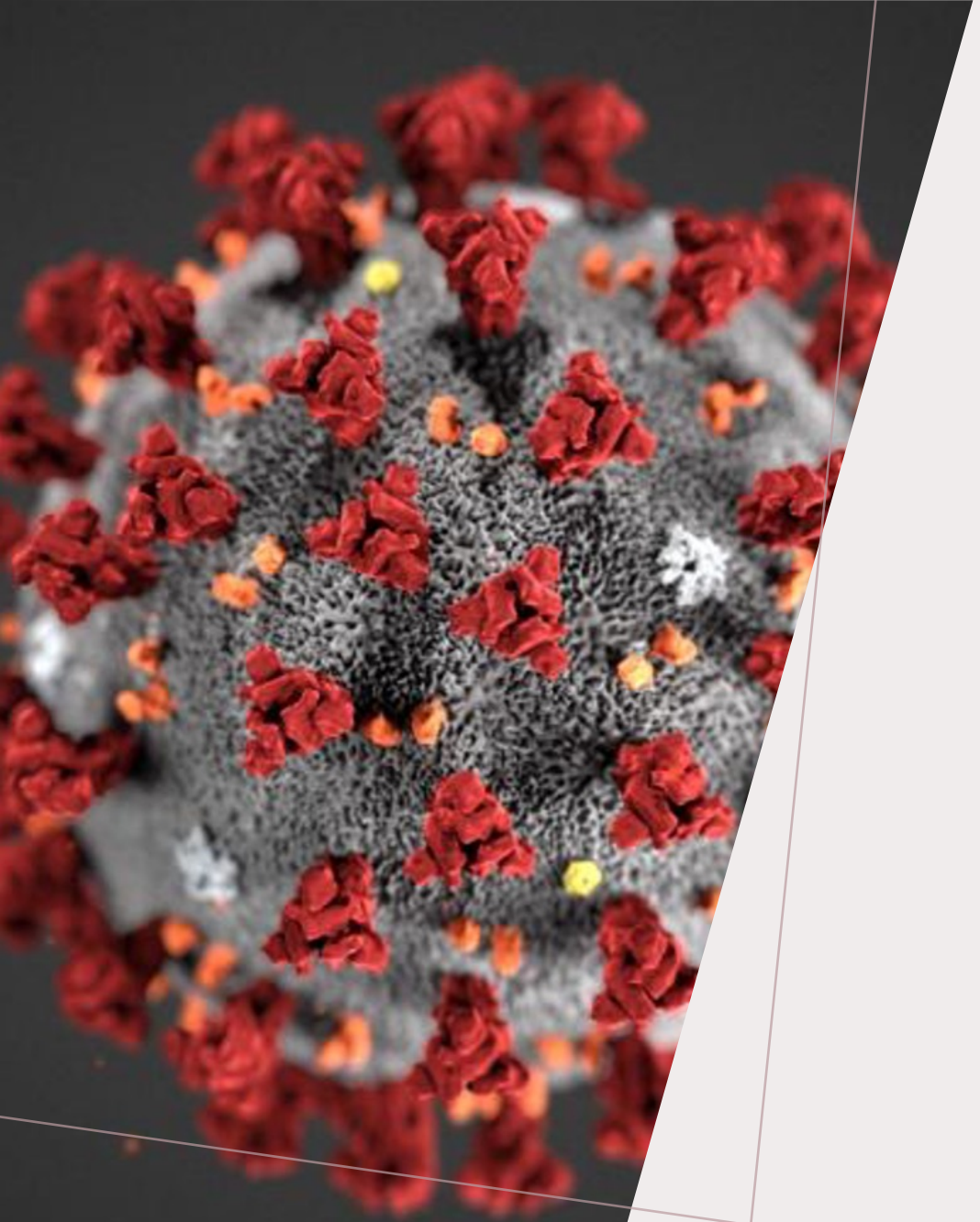
  - both mediate MBL and T-helper lymphocytes (Th-17, marker of autoimmune disease) response
  - IL-6 & TNF-α increase CD-147 receptors



- 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

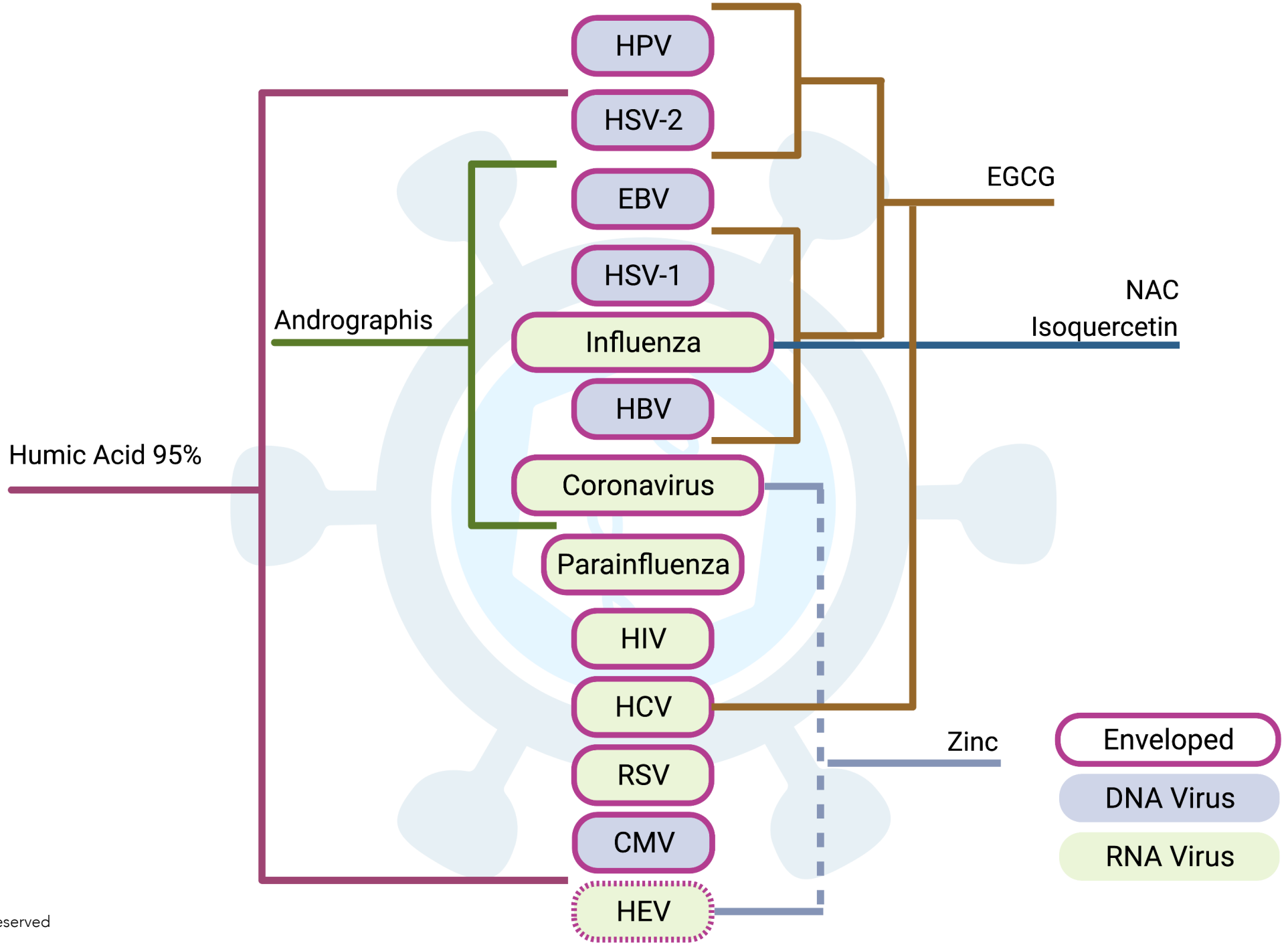


SARS-COV2 KINETICS

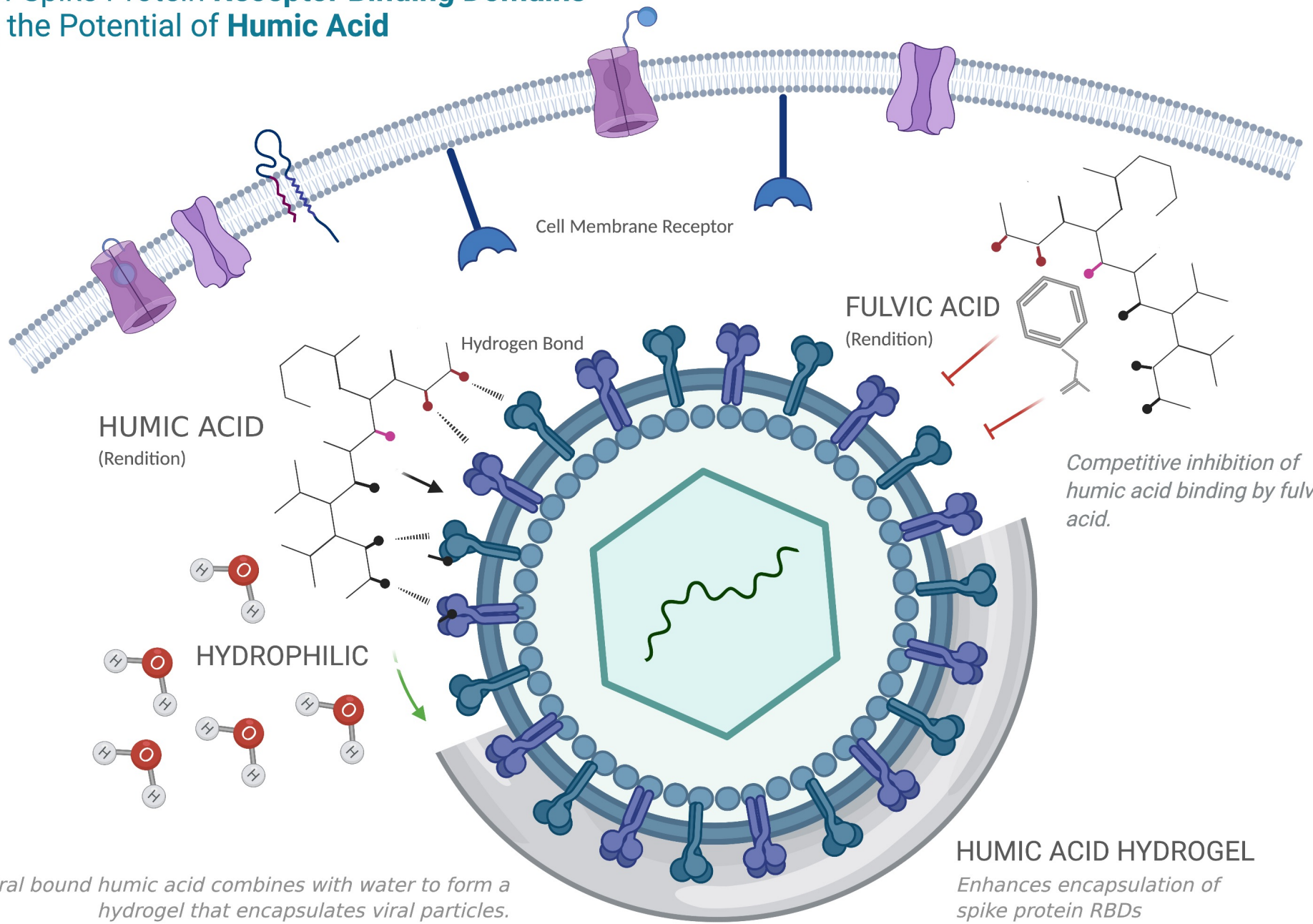
- High infectivity
  - # viral particles, 48 hours post infection, lung tissue: 3.20x > CoV2 vs. CoV (2003)
  - Despite higher infectivity, no significant induction of interferons in lung tissue
  - CoV vs. CoV2 – upregulated 11 out of 13 inflammatory cytokines/chemokines vs. 5 of 13 for CoV2.

SOLUTIONS

FUNCTIONAL TREATMENT OPTIONS



Blockade of Spike Protein **Receptor Binding Domains** Optimizing the Potential of **Humic Acid**



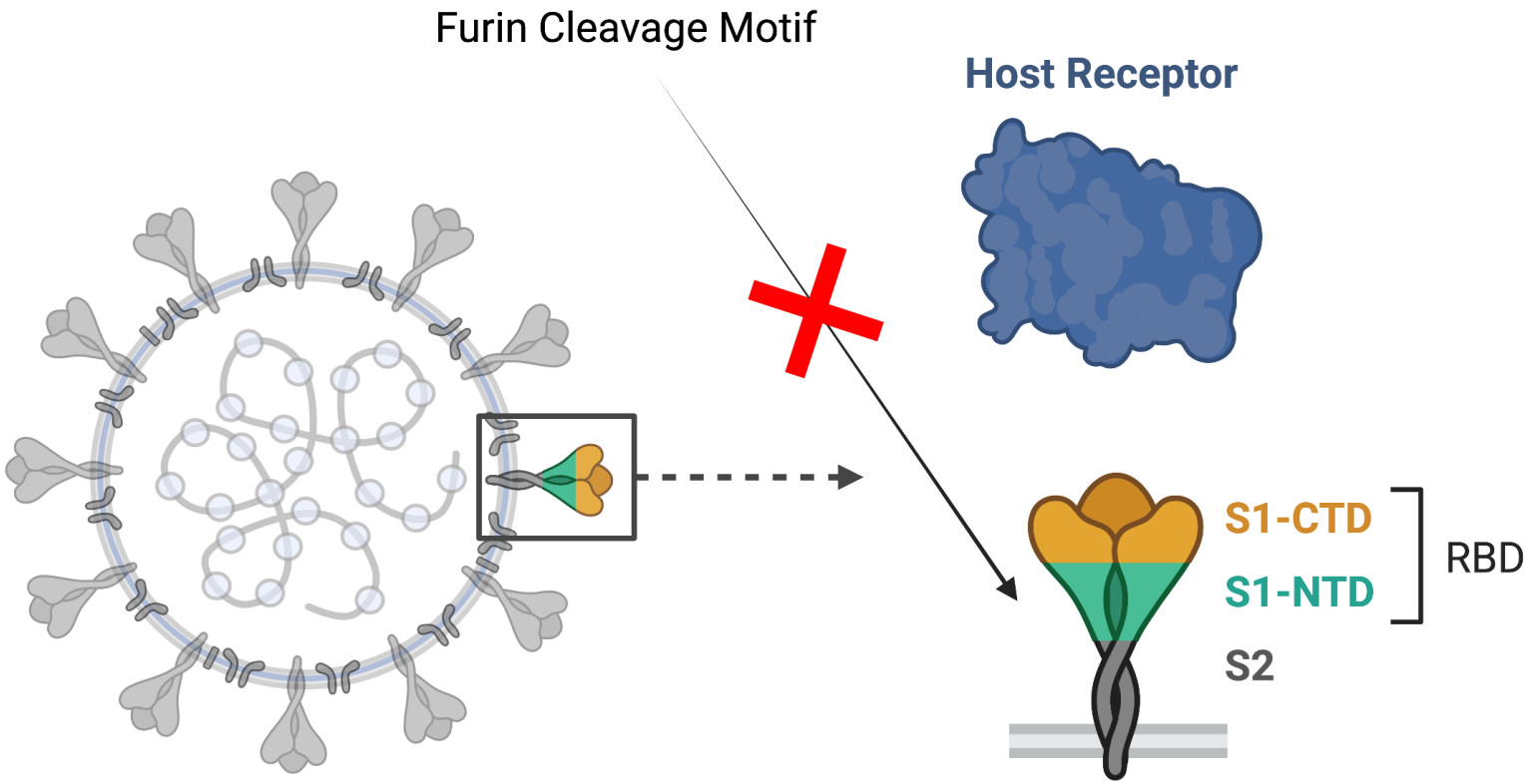
Competitive inhibition of humic acid binding by fulvic acid.

Viral bound humic acid combines with water to form a hydrogel that encapsulates viral particles.

HUMIC ACID HYDROGEL

Enhances encapsulation of spike protein RBDs

ANDROGRAPHIS
FURIN PROTEASE INHIBITOR



DUAL FUNCTION

ANTI-VIRAL & ANTI-INFLAMMATORY

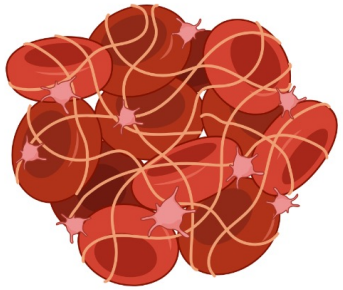
MOLECULE	CYTOKINE	INFLAMMASOME
Andrographis	CCL2 TNF-α IL-1β IL-6	NLRP3
EGCG	IL-1β (conflicting data) TNF-α (conflicting data)	NLRP3
Humic Acid 95%	TNF-α	
Quercetin	IL-1β TNF-α (Augmented by ascorbic acid)	NLRP3
Zn*	IL-1β **IL-6** IL-2 **TNF-α**	

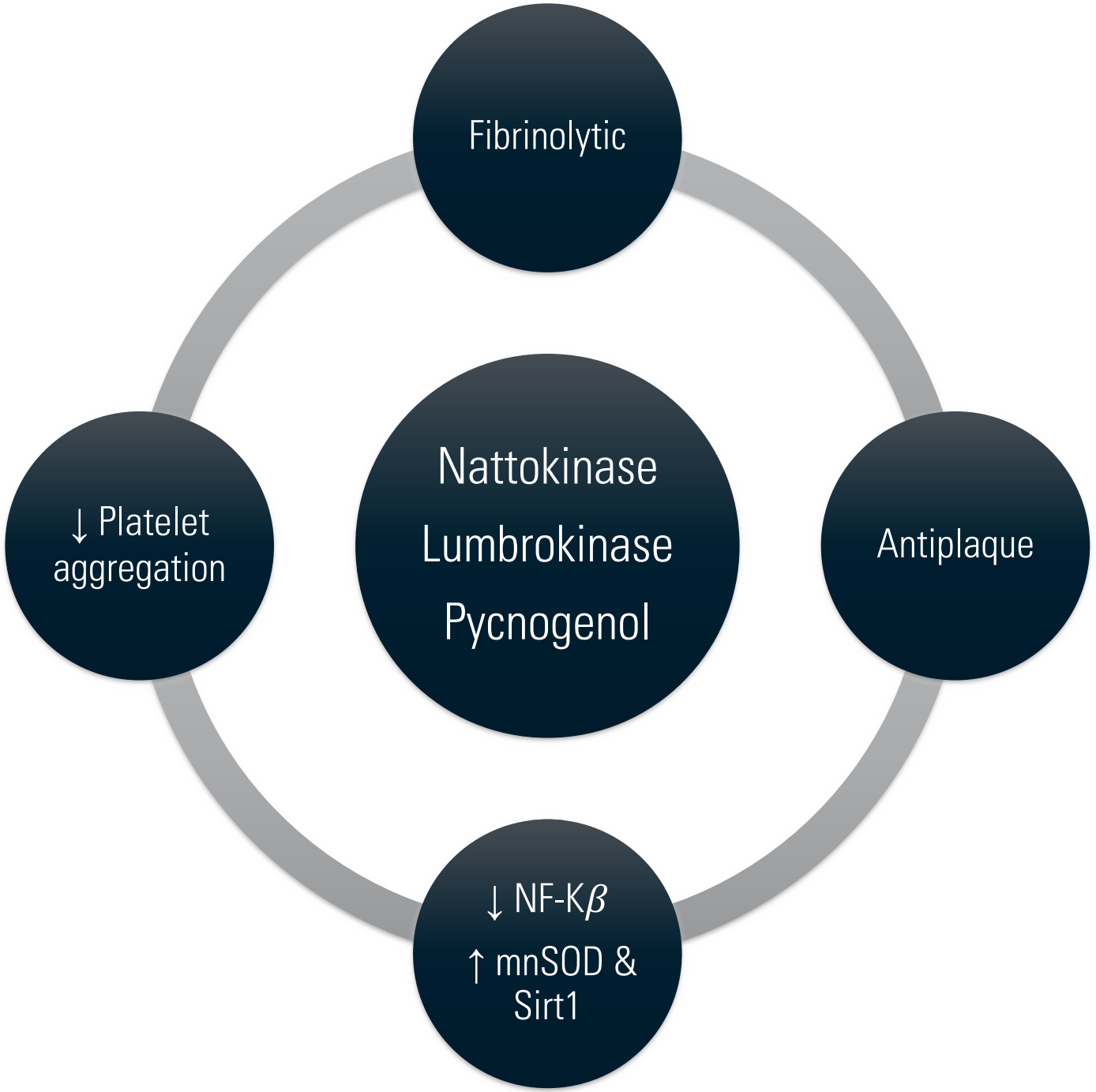
TARGETED FUNCTION

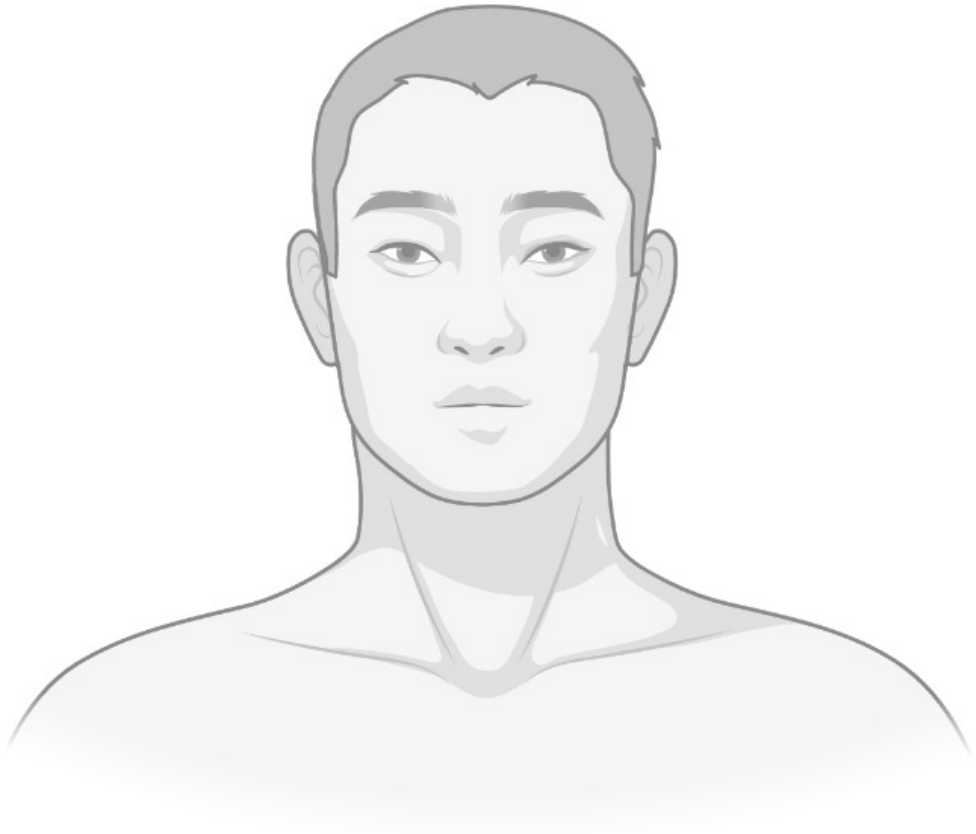
ANTI-INFLAMMATORY

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

FIBRINOLYTICS

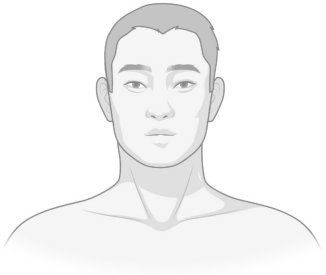






PATIENT X

- 48 y/o Caucasian
- TBF = 6.2%: ABF = 5.1%
- A1c = 5.4%
- Vitamin D = 32 mg/dL; Zn = 126 ng/dL
- TT= 962 ng/dL; FT= 172 ng/dL
- No autoimmune disease. Not ApoE4.
- Inflammatory SNPs
  - NLRP3, CARD8, CCL2 & TNF-a
  - IL-1B
- Hypercoagulability
  - Factor V Non-Leiden
  - Protein C



CARE

VIRAL INFECTION

INFLAMMATION

THROMBOSIS

VITAMIN D

ANDROGRAPHIS
ASTRALAGUS
95% HUMIC ACID

LUMBROKINASE

HIGH RISK PATIENT

- 85 y/o woman, lives alone
- **Comorbidities** – overfat, prediabetic, reactive airway disease, dyslipidemia
- **Diagnosis --** Bilateral COVID Pneumonia
- **O_2 Saturation --** mid-80's to low 90's on our engagement
- **Cough** – "barking seal"
- **Speech** – Hard to carry on a conversation
- **FHx** – Stroke

- **Treatment**
  - PRIOR: Azithromycin – 1 week prior to additional intervention
  - NEW: Humic Acid 95% + Resolvins
- **Outcome**
  - Vacuuming her home, 24-hours after intervention
- **Vaccination Status**
  - S/P 2 injections, Moderna
  - Second dose was within 3 months of a symptomatic infection

MED-LEGAL

- MALPRACTICE
- “PHARMACOGENOIMCS”

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@SOCOLMD.COM

- Slides 9, 10, 11, 21, 24, 25, 30, *36, 38*, 42, 44, 45, 47 -- Graphics "Created with BioRender.com"
- Bousoik, E, Montazaeri A, Do We Know Jack About JAK? A Closer Look at JAK/STAT Signaling Pathway, Frontiers in Oncology, Vol 8, 2018. DOI=10.3389/fonc.2018.00287
- Liu, T., Zhang, L., Joo, D. *et al.* NF-κB signaling in inflammation. *Sig Transduct Target Ther* **2,** 17023 (2017). https://doi.org/10.1038/sigtrans.2017.23
- Nakatsumi et al., 2017, Cell Reports 21, 2471–2486, November 28, 2017. https://doi.org/10.1016/j.celrep.2017.11.014
- Chambers, P.W. (2022) COVID-19: From Cough to Coffin. *Open Access Library Journal*, **9**, 1-24. doi: 10.4236/oalib.1108300
- Vinciguerra M, Greco E. Sars-CoV-2 and black population: ACE2 as shield or blade?. *Infect Genet Evol*. 2020;84:104361. doi:10.1016/j.meegid.2020.104361
- Beohar N, Damaraju S, Prather A, Yu QT, Raizner A, Kleiman NS, Roberts R, Marian AJ. Angiotensin-I converting enzyme genotype DD is a risk factor for coronary artery disease. J Investig Med. 1995 Jun;43(3):275-80. PMID: 7614074.
- Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B, Jacobson D. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. Elife. 2020 Jul 7;9:e59177. doi: 10.7554/eLife.59177. PMID: 32633718; PMCID: PMC7410499.
- Al-Hinai AT, Hassan MO, Simsek M, Al-Barwani H, Bayoumi R. Genotypes and allele frequencies of angiotensin converting enzyme (ACE) insertion/deletion polymorphism among Omanis. *J Sci Res Med Sci*. 2002;4(1-2):25-27.
- Benjamin Ollomo, Laurianne Yacka Mouélé, Berthold Bivigou-Mboumba, Bertrand Mve Ondo, Elisabeth Lendoye et al. (2019) D Allele and DD Genotype of I /D Polymorphism in The ACE Gene in Patients with Hypertension, Stroke And Cancer Prostate In Libreville: A Concern Given The High Frequencies of these Signatures in Gabonese Population. *Journal Of Proteomics And Genomics Research* - 2(3):3-12.
- 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

THANK YOU

PLEASE REACH OUT WITH YOUR QUESTIONS TO:

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