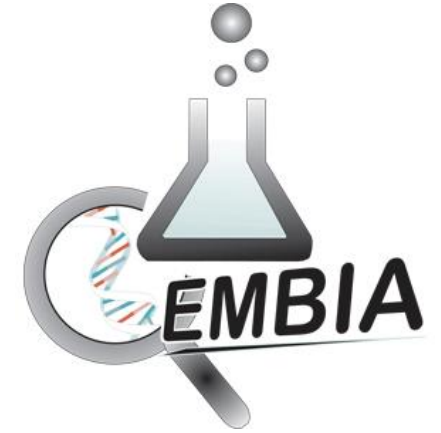




ΠΑΝΕΠΙΣΤΗΜΙΟ
ΠΑΤΡΩΝ
UNIVERSITY OF PATRAS



Nicotinic Cholinergic Pathway and COVID-19

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The National inspired-RIs on

Integrated Structural Biology,
Drug Screening Efforts &
Drug target functional characterization

Δημόσια Δαπάνη: € 3.818.820,00

Θεματικός Τομέας RIs: Υγεία και Φάρμακα

Συμμετέχοντες Φορείς:

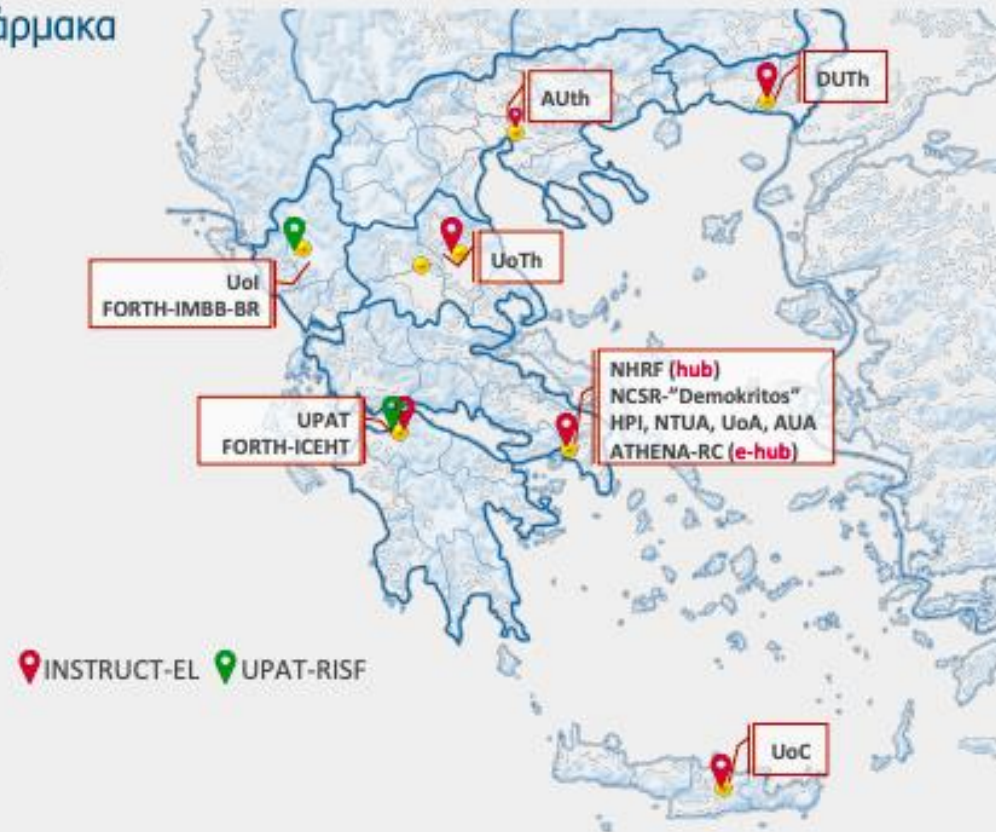
Ερευνητικά Κέντρα

1. Εθνικό Ίδρυμα Ερευνών (Συντονιστής, **Hub**)*
2. Εθνικό Κέντρο Έρευνας Φυσικών Επιστημών – «Δημόκριτος»
3. ΙΤΕ - Ινστιτούτο Επιστημών Χημικής Μηχανικής
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12. Πανεπιστήμιο Κρήτης
13. Δημοκρίτειο Πανεπιστήμιο Θράκης
14. Εθνικό Μετσόβιο Πολυτεχνείο

* Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, μέσω του ΕΙΕ



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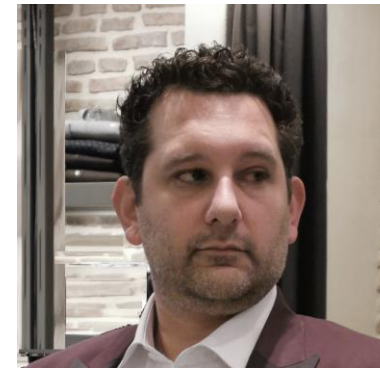
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Nikolaos Alexandris
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Stahis Giotis
Imperial College London



Konstantinos Poulas
University of Patras

COVID-19 and smoking/vaping

REUTERS Business Markets World Politics TV More

HEALTH NEWS MARCH 8, 2020 / 8:58 PM / 3 MONTHS AGO

Smoking or vaping increases risks for those with coronavirus: NYC mayor

1 MIN READ  



FILE PHOTO: New York City Mayor Bill de Blasio is seen at a news briefing in the Manhattan borough of New York City, New York, U.S., March 2, 2020. REUTERS/Andrew Kelly/File Photo

Smokers and Vapers May Be at Greater Risk for Covid-19

Tobacco and marijuana products damage lungs, where the virus does its harm. Health officials are urging people to quit, and temporary sales bans are even being discussed.



"Clean air is what the lungs should be inhaling, especially during a global pandemic," said one doctor. Antonio Perez/Chicago Tribune, via Alamy Live News

 APRIL 29, 2020

Smoking may explain why more men than women die of COVID-19 in Spain

by Universitat Oberta de Catalunya




Κάπνισμα και COVID-19

- Οι καπνιστές υπο-εκπροσωπούνται μεταξύ των νοσηλευομένων από COVID-19
- Οι καπνιστές έχουν μικρότερη πιθανότητα να διαγνωστούν από COVID-19
- Οι καπνιστές έχουν μεγαλύτερη πιθανότητα να αναπτύξουν σοβαρή νόσο ΕΦ΄ ΟΣΟΝ νοσηλευθούν
- Το κάπνισμα είναι επιβαρυντικός παράγοντας για βαριά νόσο μεταξύ του μικρού ποσοστού των καπνιστών που θα αναπτύξουν βαριά νόσο και που θα απαιτήσει νοσηλεία



Current smoking, former smoking, and adverse outcome among hospitalized COVID-19 patients: a systematic review and meta-analysis

Konstantinos Farsalinos , Anastasia Barbouni, Konstantinos Poulas, Riccardo Polosa , Pasquale Caponnetto and Raymond Niaura



EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory-confirmed COVID-19 cases

Theodoros V. Giannouchos, Roberto A. Sussman, José M. Mier, Konstantinos Poulas, Konstantinos Farsalinos

Ther Adv Chronic Dis

2020, Vol. 11: 1–14

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2040622320935765

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International Journal of
*Environmental Research
and Public Health*



Article

A Systematic Review and Meta-Analysis of Hospitalised Current Smokers and COVID-19

Jesus González-Rubio ^{1,†} , Carmen Navarro-López ², Elena López-Nájera ^{3,†}, Ana López-Nájera ⁴, Lydia Jiménez-Díaz ^{5,*,†} , Juan D. Navarro-López ^{5,*,†}  and Alberto Nájera ^{1,*,†} 

The number of hospitalised smokers was smaller than expected based on the smoking prevalence in the different countries. The meta-analysis results obtained in China, the US and Italy indicated that a smoking habit lowers the likelihood of being hospitalised by COVID-19.

Κάπνισμα και COVID-19

- Οι καπνιστές υπο-εκπροσωπούνται μεταξύ των νοσηλευομένων από COVID-19
 - Οι καπνιστές έχουν μικρότερη πιθανότητα να διαγνωστούν από COVID-19
 - Οι καπνιστές έχουν μεγαλύτερη πιθανότητα να αναπτύξουν σοβαρή νόσο ΕΦ' ΟΣΟΝ νοσηλευθούν
 - Το κάπνισμα είναι επιβαρυντικός παράγοντας για βαριά νόσο μεταξύ του μικρού ποσοστού των καπνιστών που θα αναπτύξουν βαριά νόσο και που θα απαιτήσει νοσηλεία
-
- **ΓΙΑΤΙ?**



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Toxicology Reports

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



Editorial: Nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system



EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Correspondence

COVID-19 and the nicotinic cholinergic system

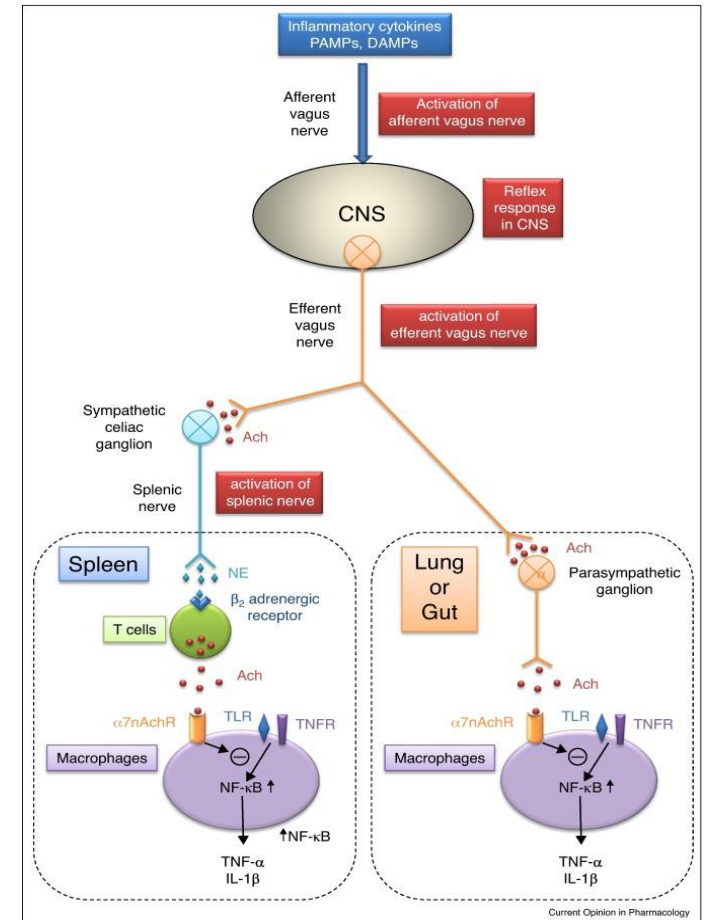
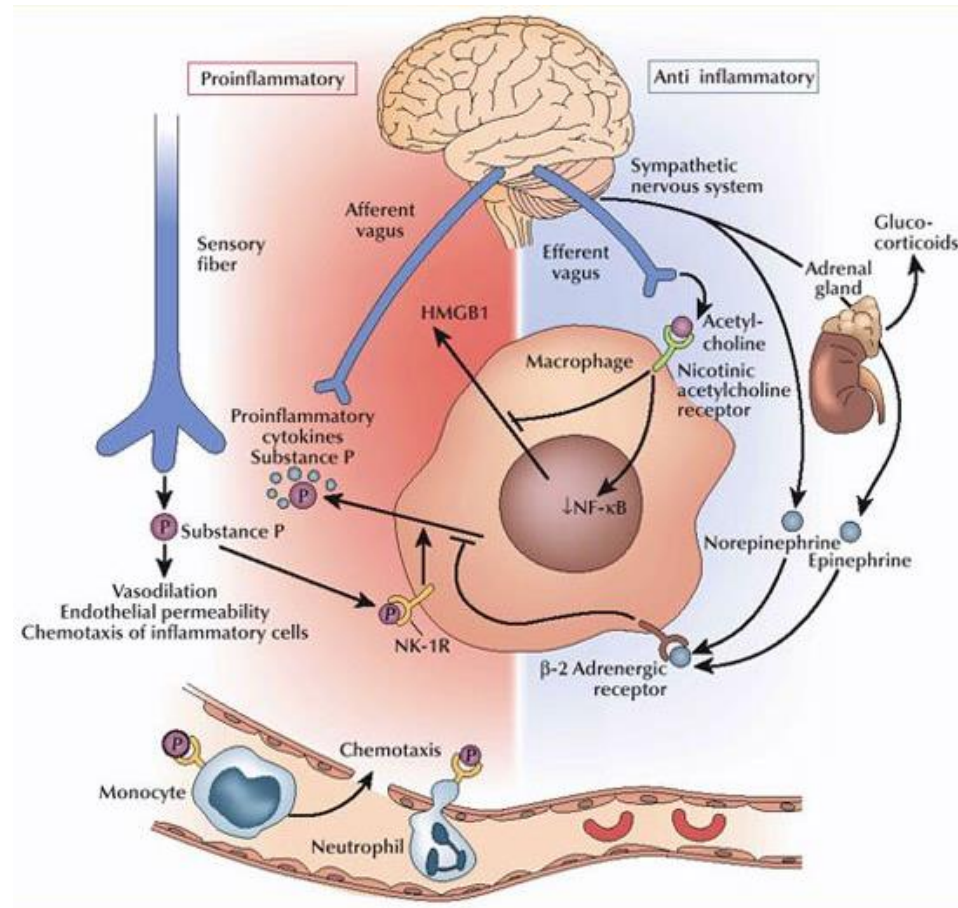
Konstantinos Farsalinos, Athina Angelopoulou, Nikos Alexandris, Konstantinos Poulas

Nicotinic receptors and SARS-CoV-2

Low smoking prevalence among hospitalized COVID-19 patients generated a new hypothesis about an interaction between SARS-CoV-2 and nicotinic cholinergic system

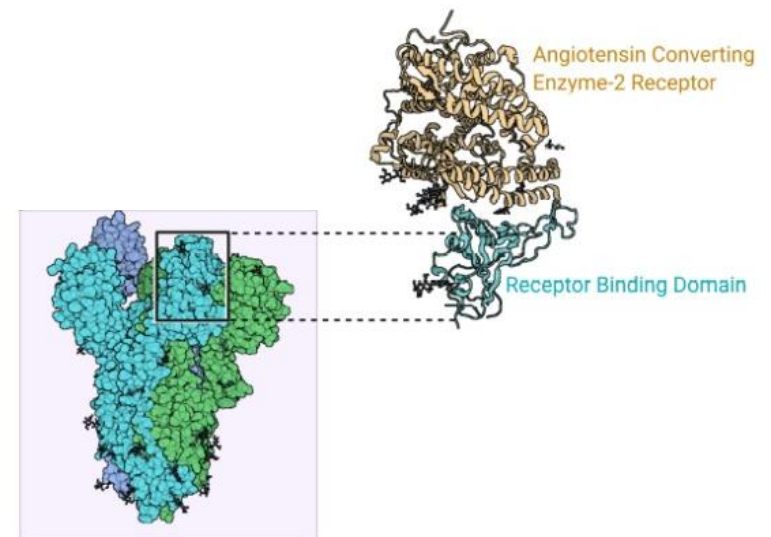
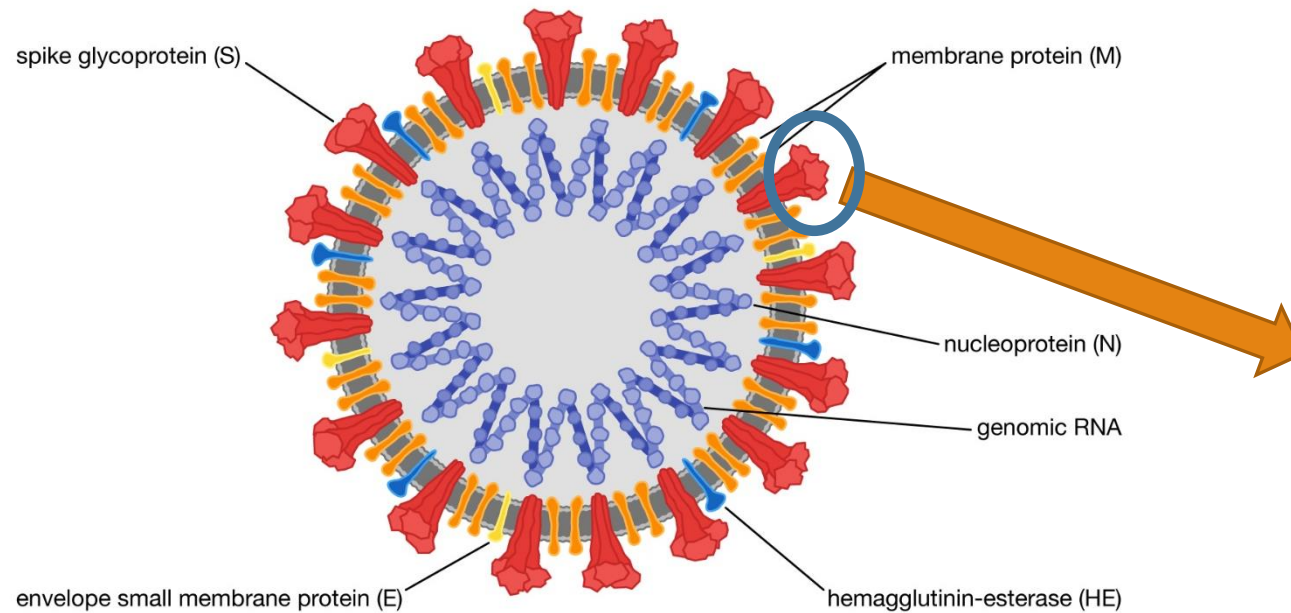
Cholinergic anti-inflammatory pathway

Matthay et al., Nature Med 2004
Yamada et al. Curr Opin Pharmacol 2018



Current Opinion in Pharmacology

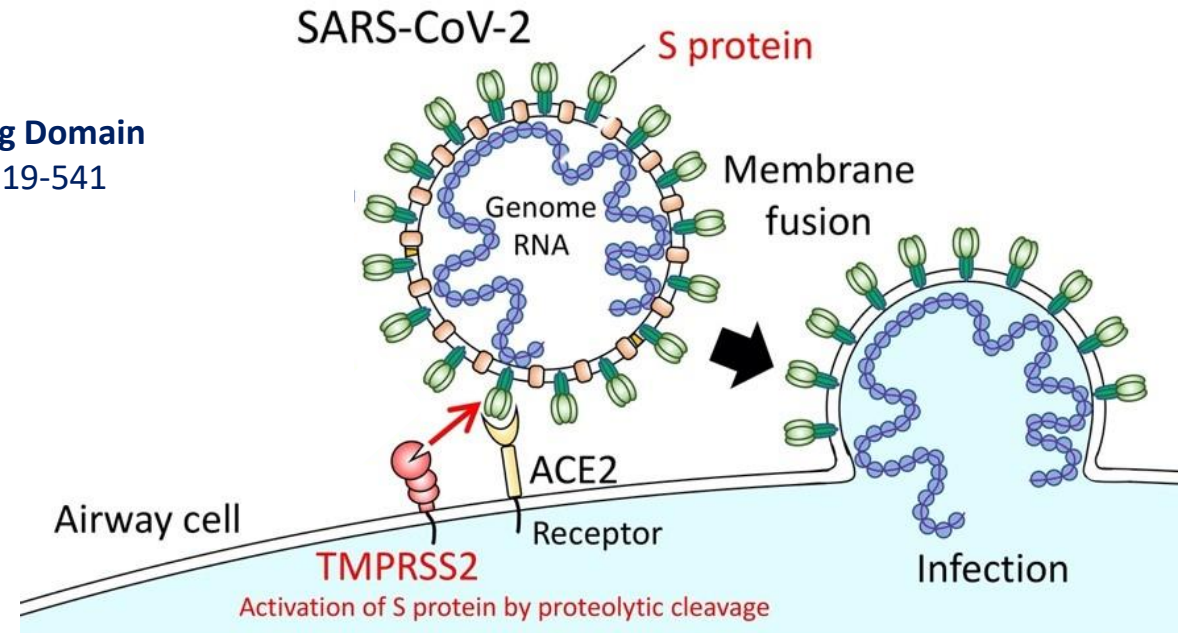
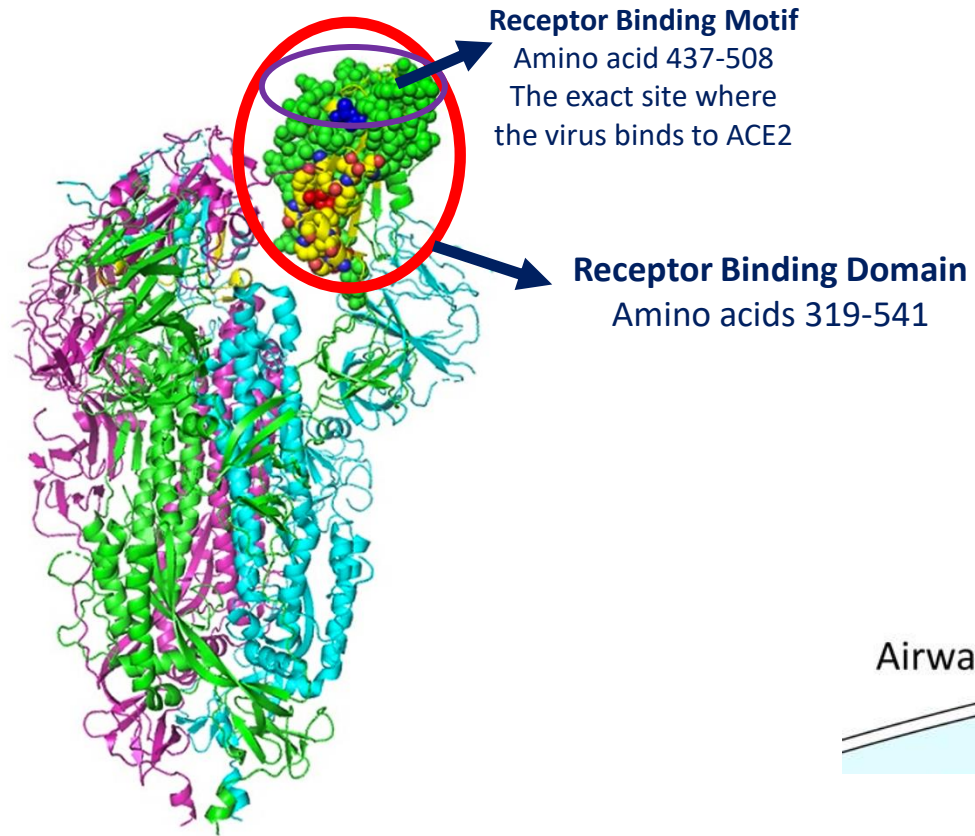
SARS-CoV-2 and ACE2



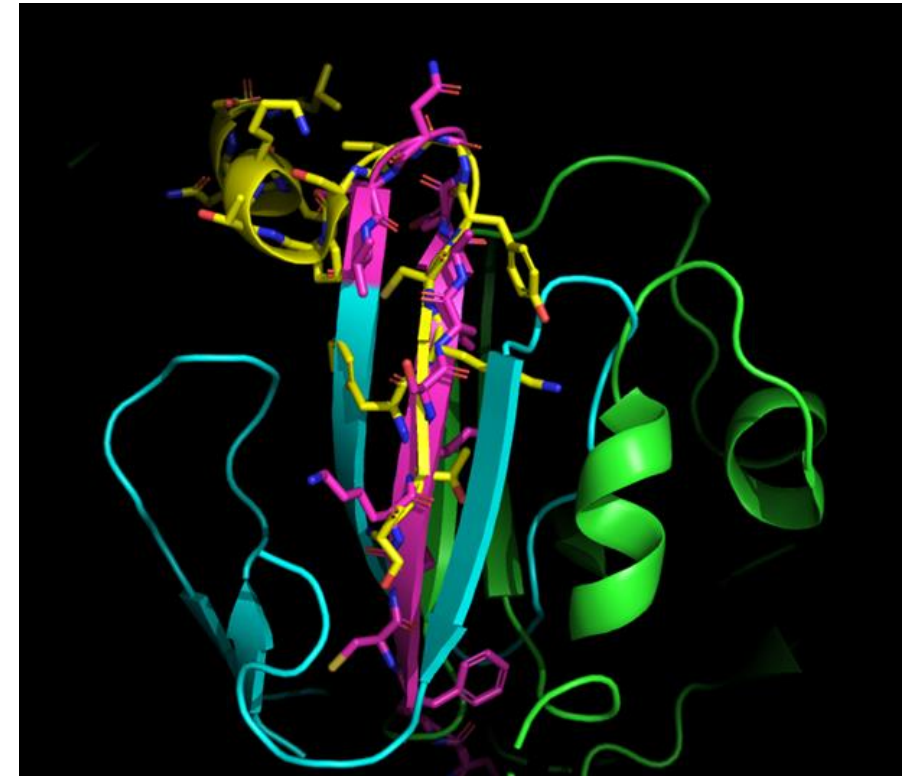
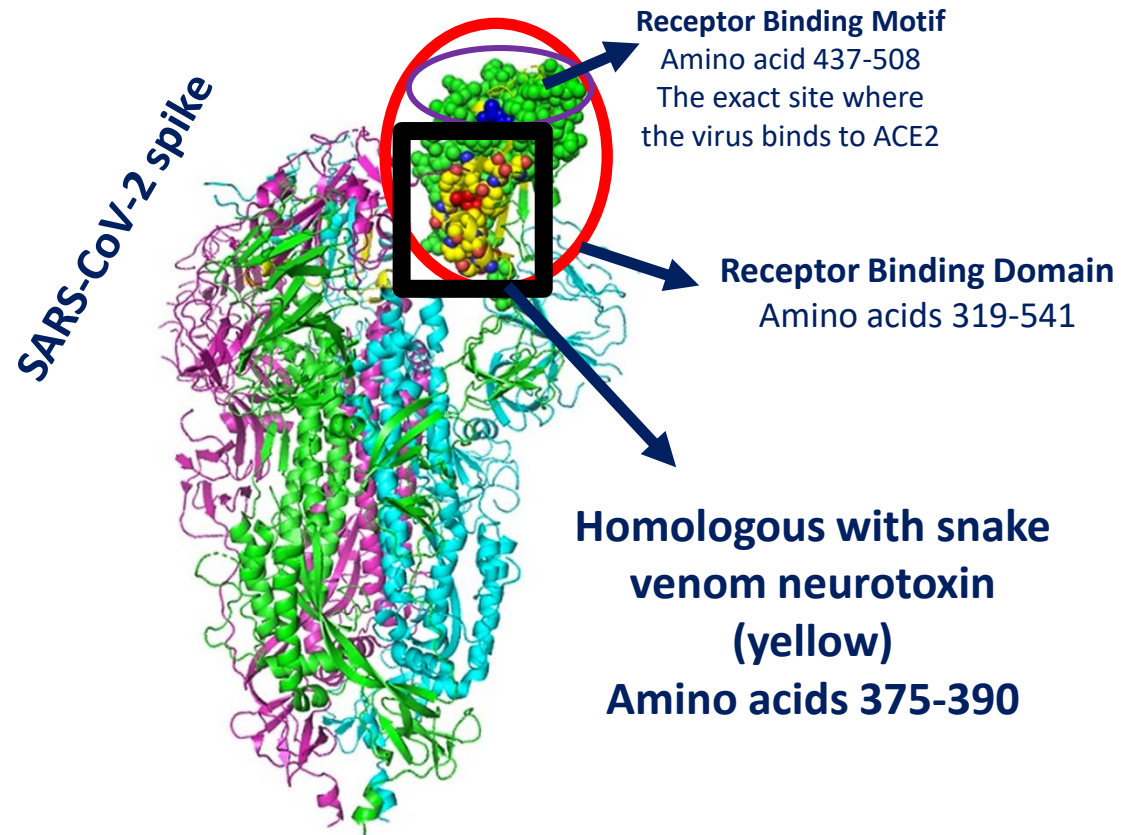
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SARS-CoV 2 Structure. Contributed by Rohan Bir Singh, MD; Made with Biorender.com. Cascella et al., STATPEARLS 2020.

SARS-CoV-2 and ACE2

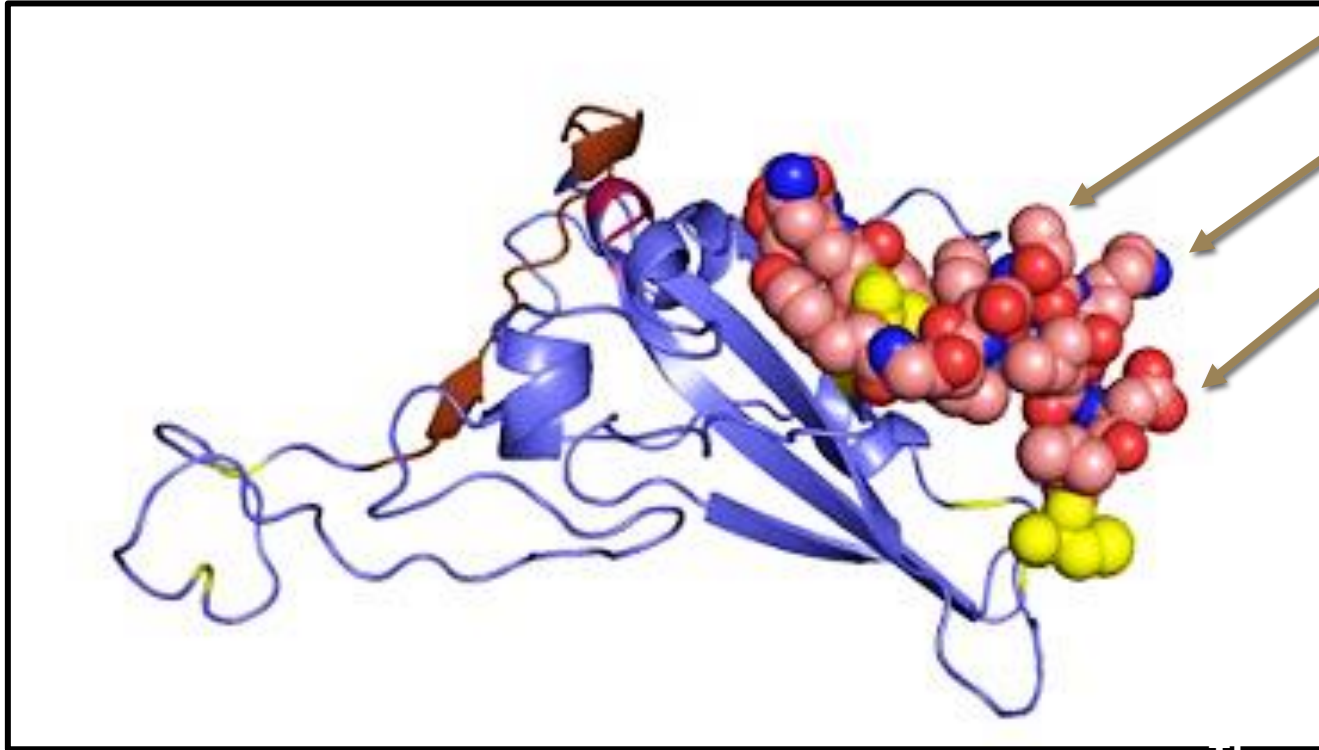


A direct interaction?

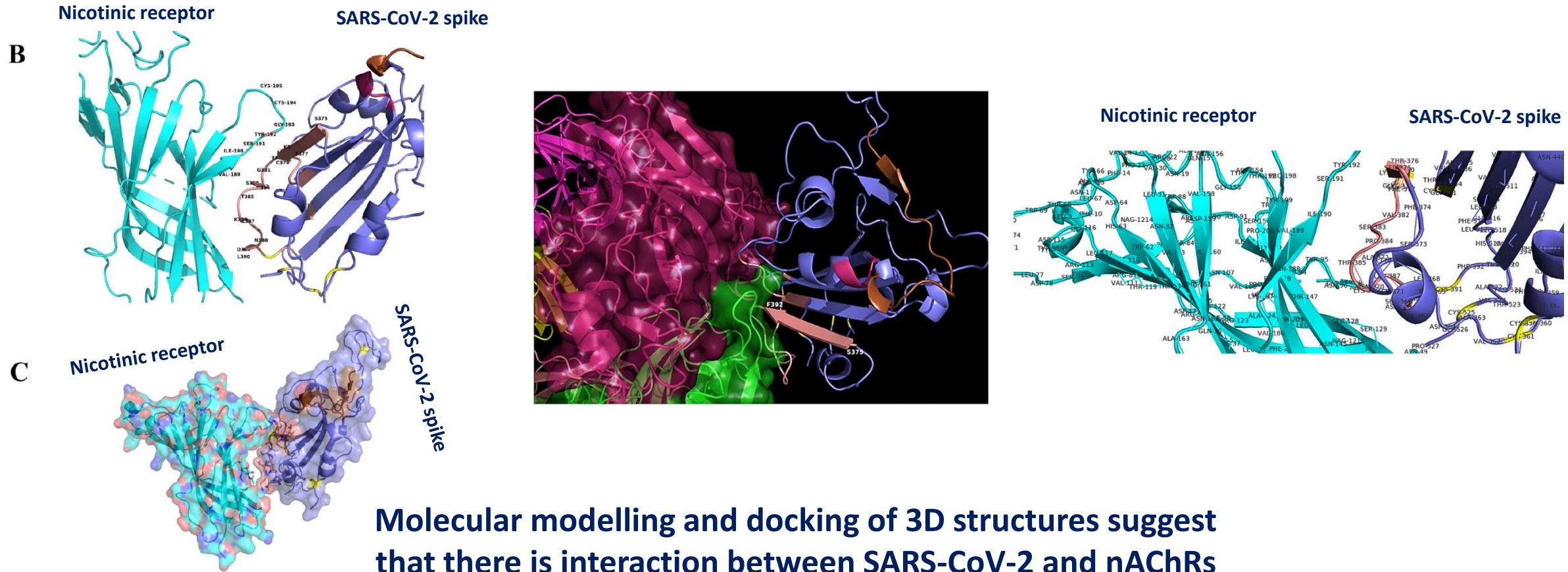


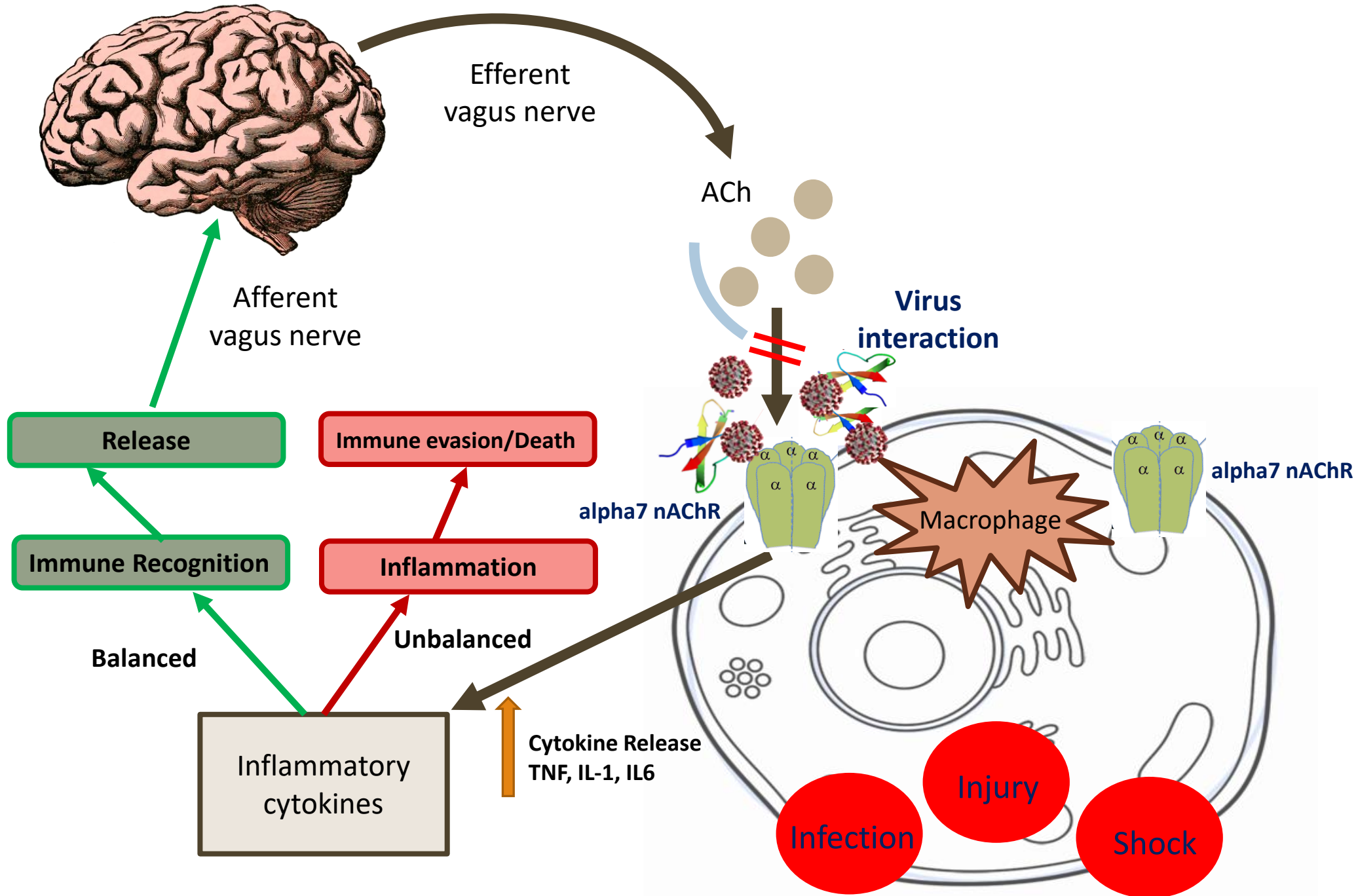
Snake venom toxins bind to nAChRs

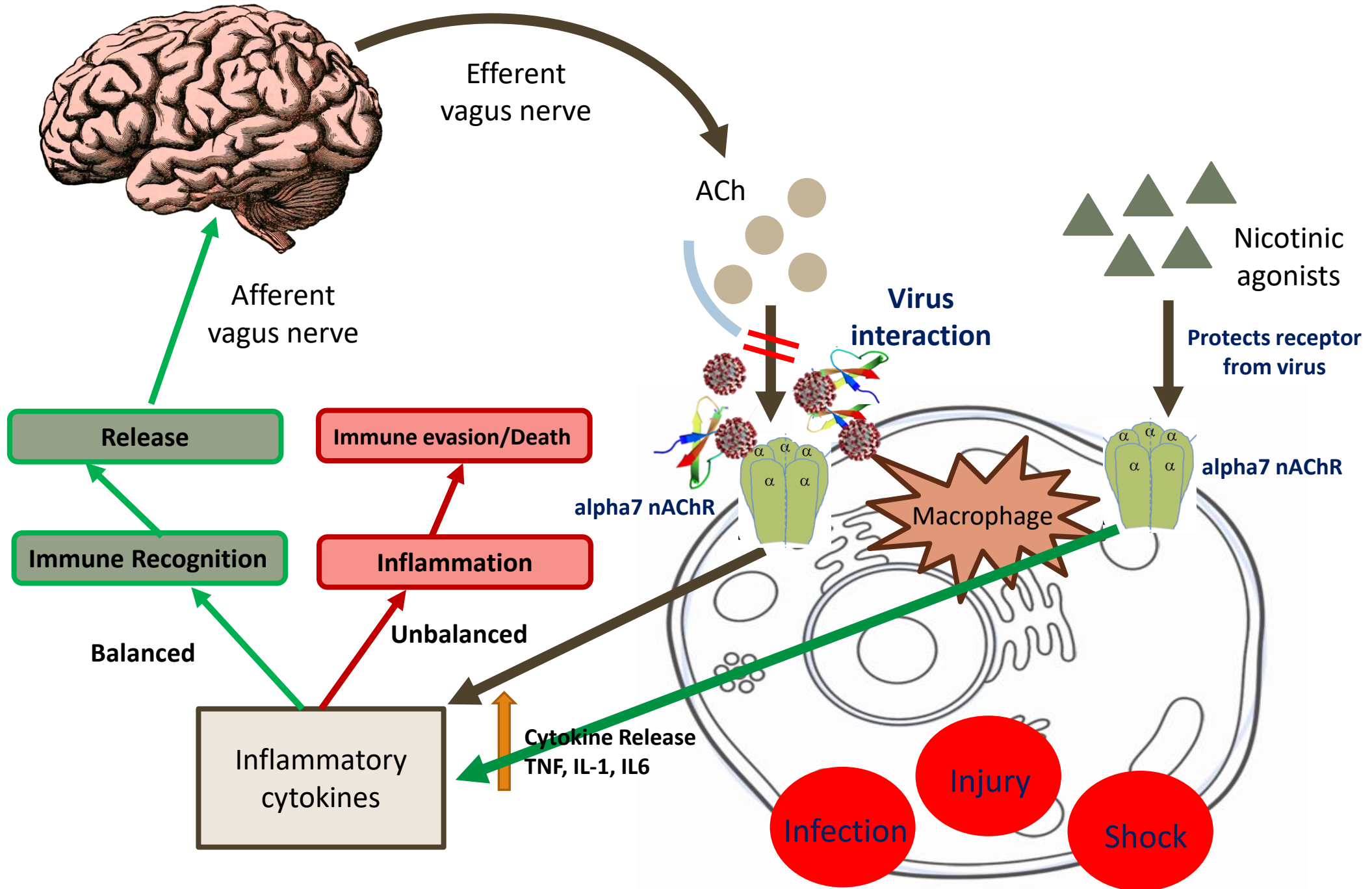
Three finger
snake toxin



A direct interaction?







Efferent
vagus nerve

Afferent
vagus nerve

ACh

Nicotinic
agonists

Virus
interaction

Protects receptor
from virus

Release

Immune evasion/Death

Immune Recognition

Inflammation

alpha7 nAChR

Macrophage

alpha7 nAChR

Balanced

Unbalanced

Inflammatory
cytokines

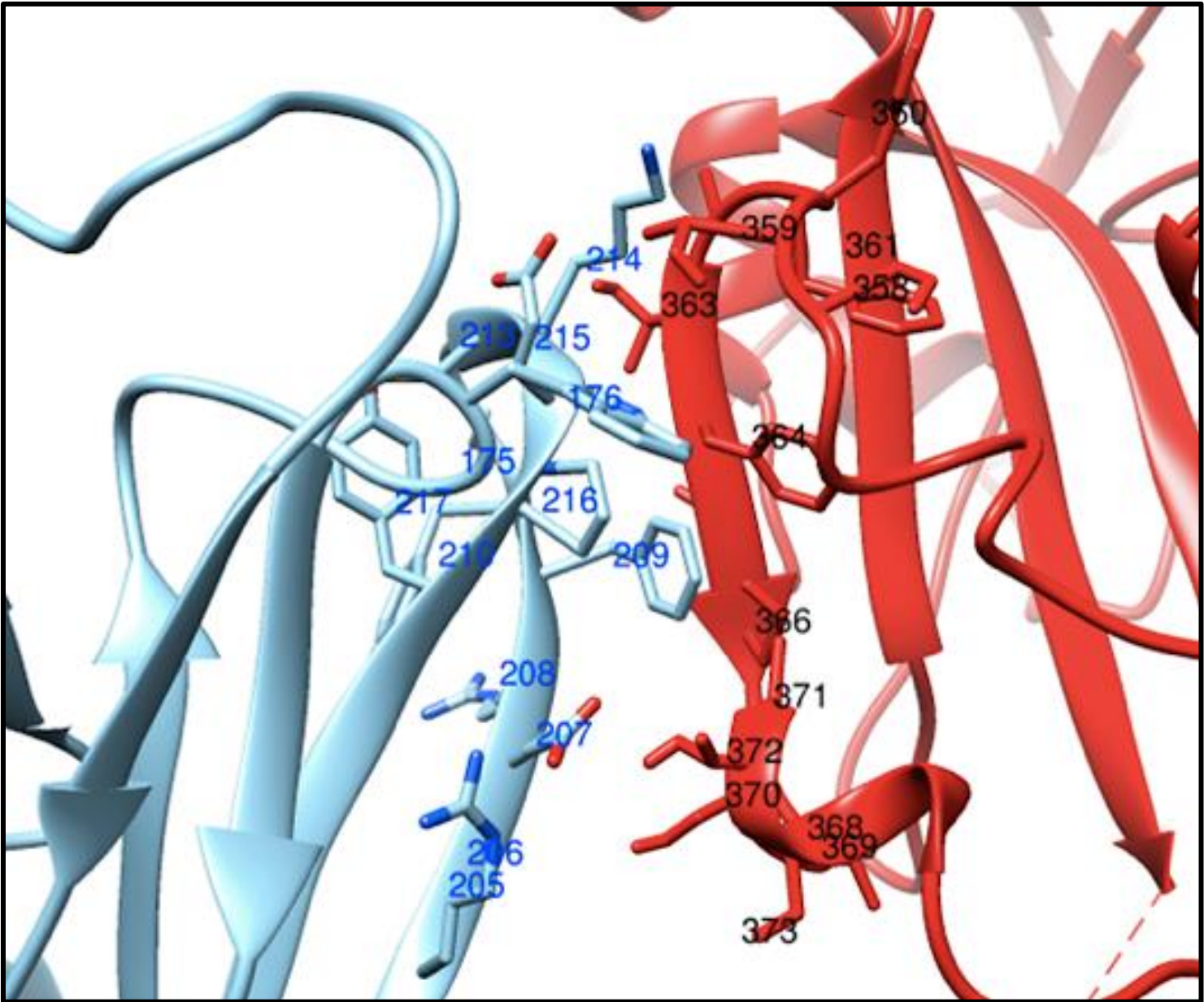
Cytokine Release
TNF, IL-1, IL6

Infection

Injury

Shock

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R

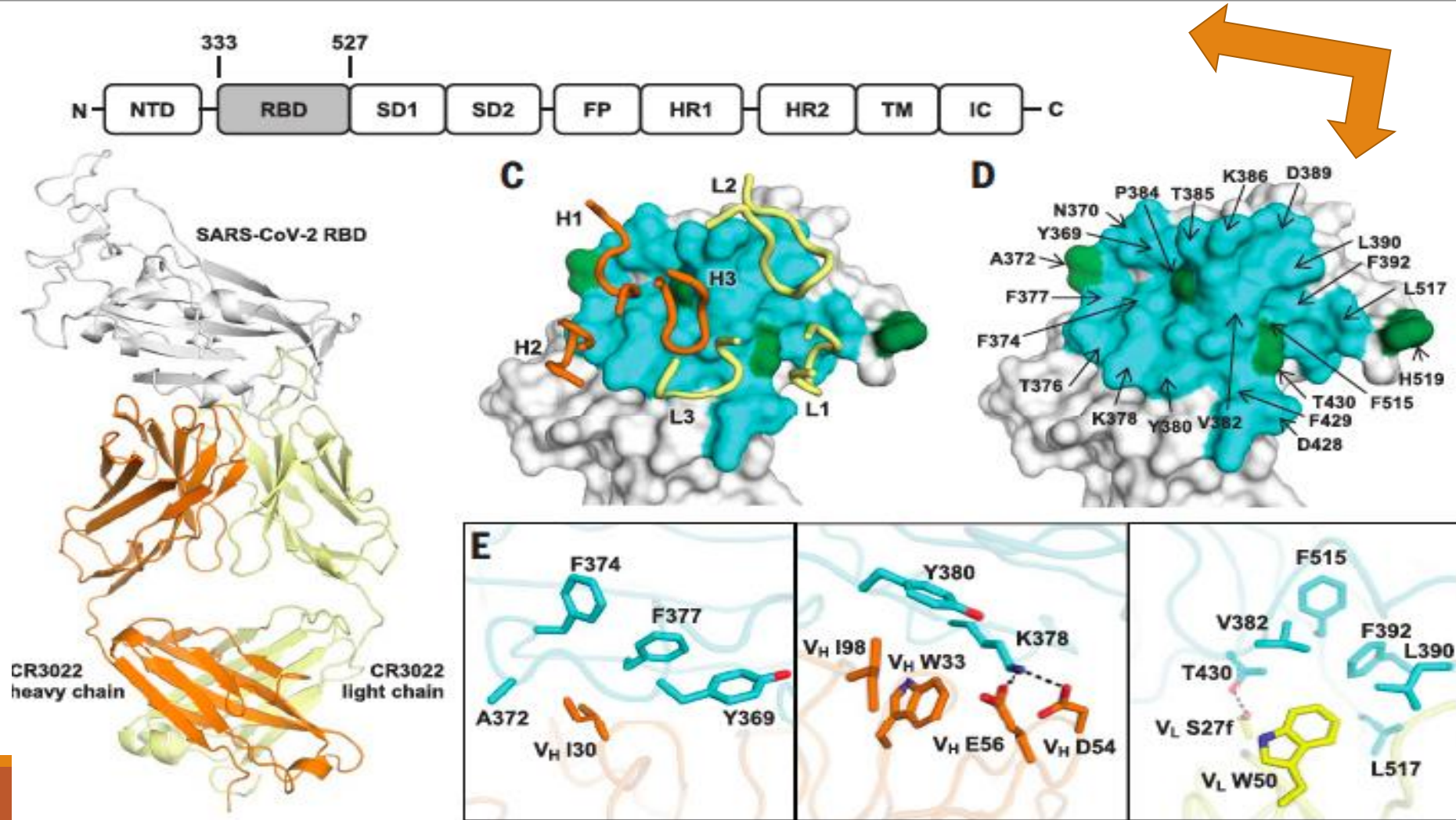


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This group has identified the binding of a human antibody to the SPIKE PROTEIN

*****THE MAIN EPITOPE IS aa 375--390*****



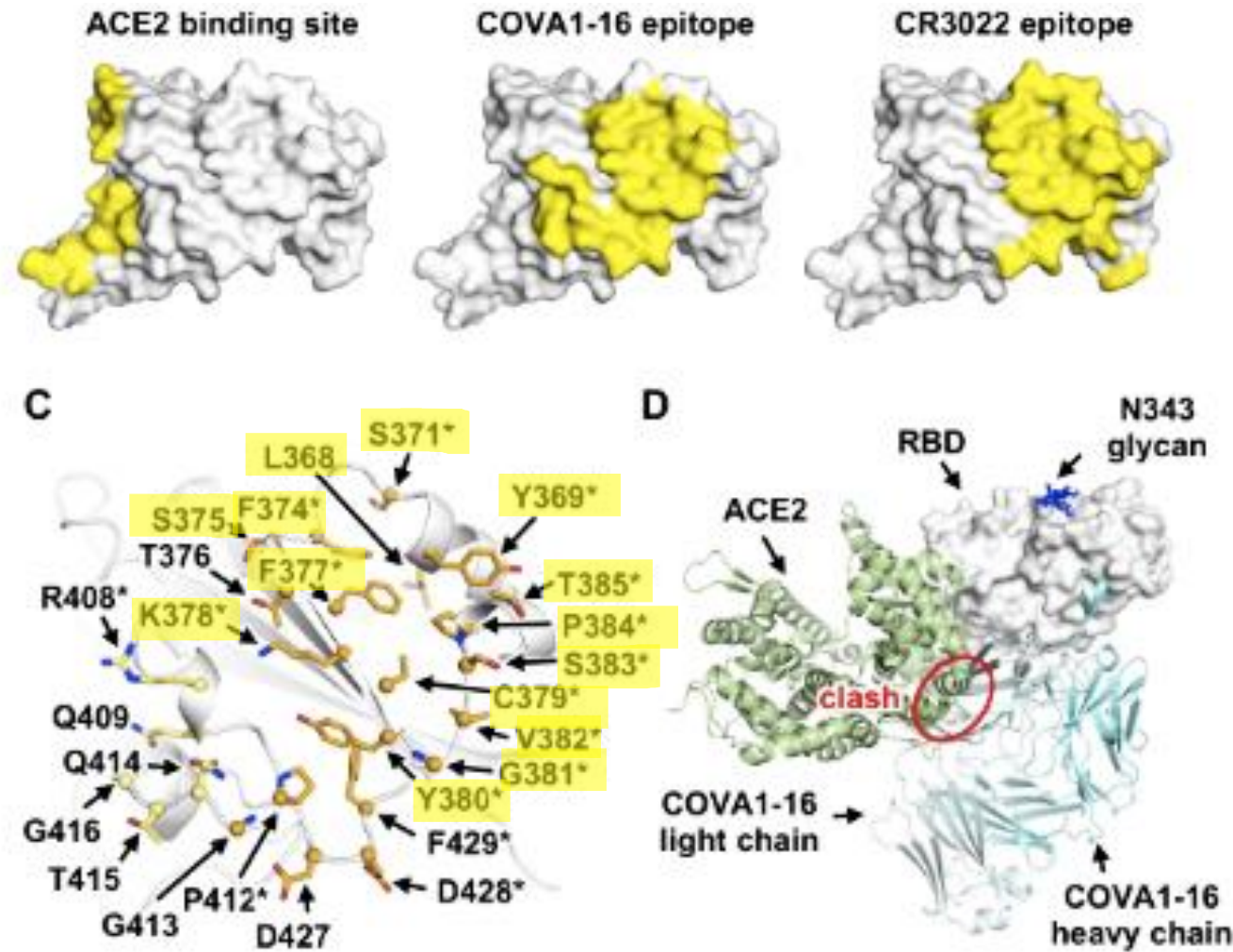
A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV

This group has identified the binding of a human antibody to the SPIKE PROTEIN

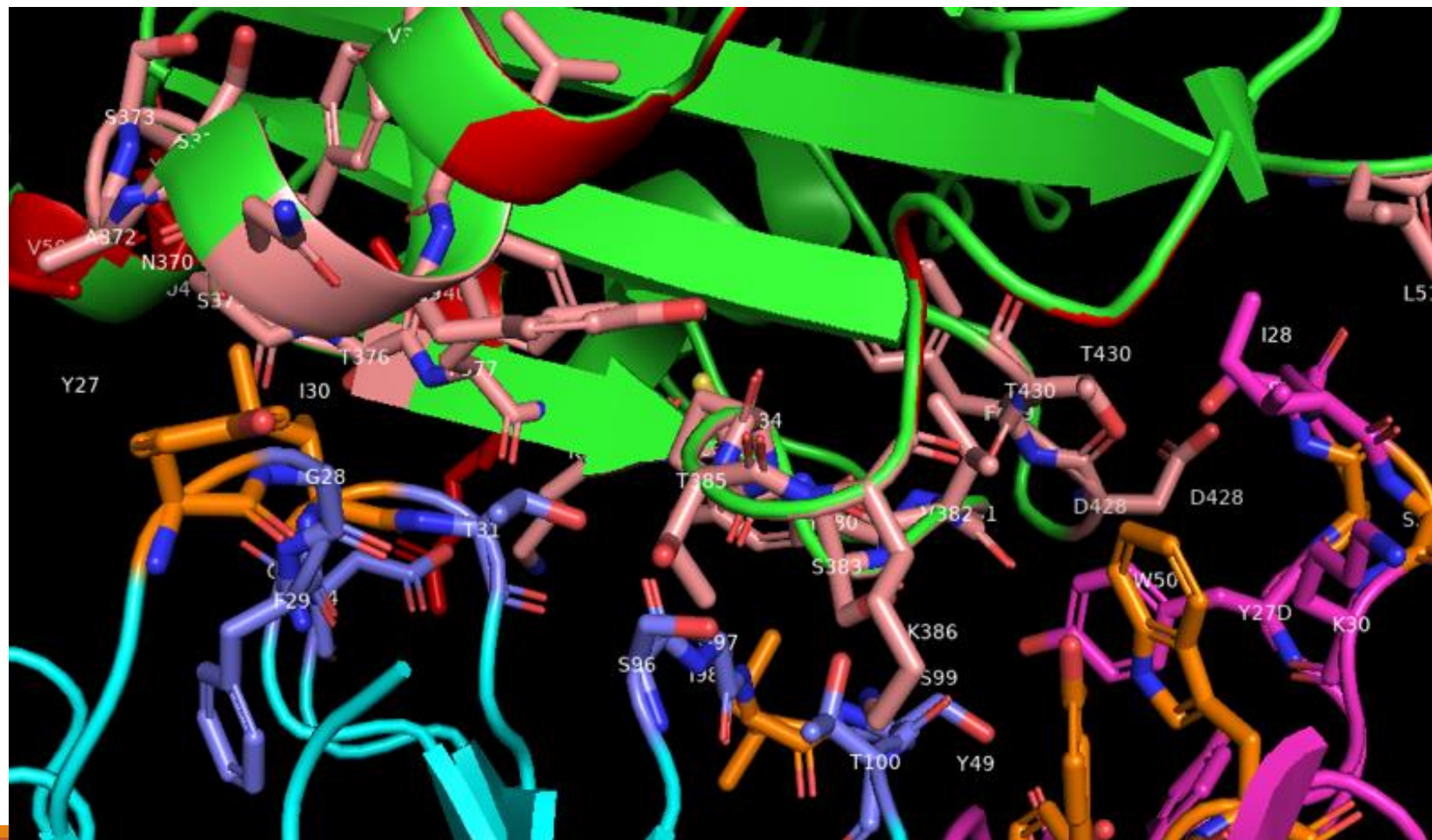
*****THE MAIN EPITOPE IS aa 375--390*****

SARS-CoV	RBD	306	RVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWERKKISNCVADYSVL	355
SARS-CoV-2	RBD	319	RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVL	368
SARS-CoV	RBD	356	YNSTFFSTFKCYGVSATKLNDLCFSNVYADSFVVKGDDVRQIAPGQTGVI	405
SARS-CoV-2	RBD	369	YNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKI	418
SARS-CoV	RBD	406	ADYNYKLPDDFMGCVLAWNTRNIDATSTGNHNYKYRYLRHGKLRPFERDI	455
SARS-CoV-2	RBD	419	ADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDI	468
SARS-CoV	RBD	456	SNVPFSPDGKPCTP-PALNCYWPLNDYGFYTTTGIGYQPYRVVLSFELL	504
SARS-CoV-2	RBD	469	STEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELL	518
SARS-CoV	RBD	505	NAPATVCGPKLSTDLIKNQCVNF	528
SARS-CoV-2	RBD	519	HAPATVCGPKKSTNLVKNKCVNF	541

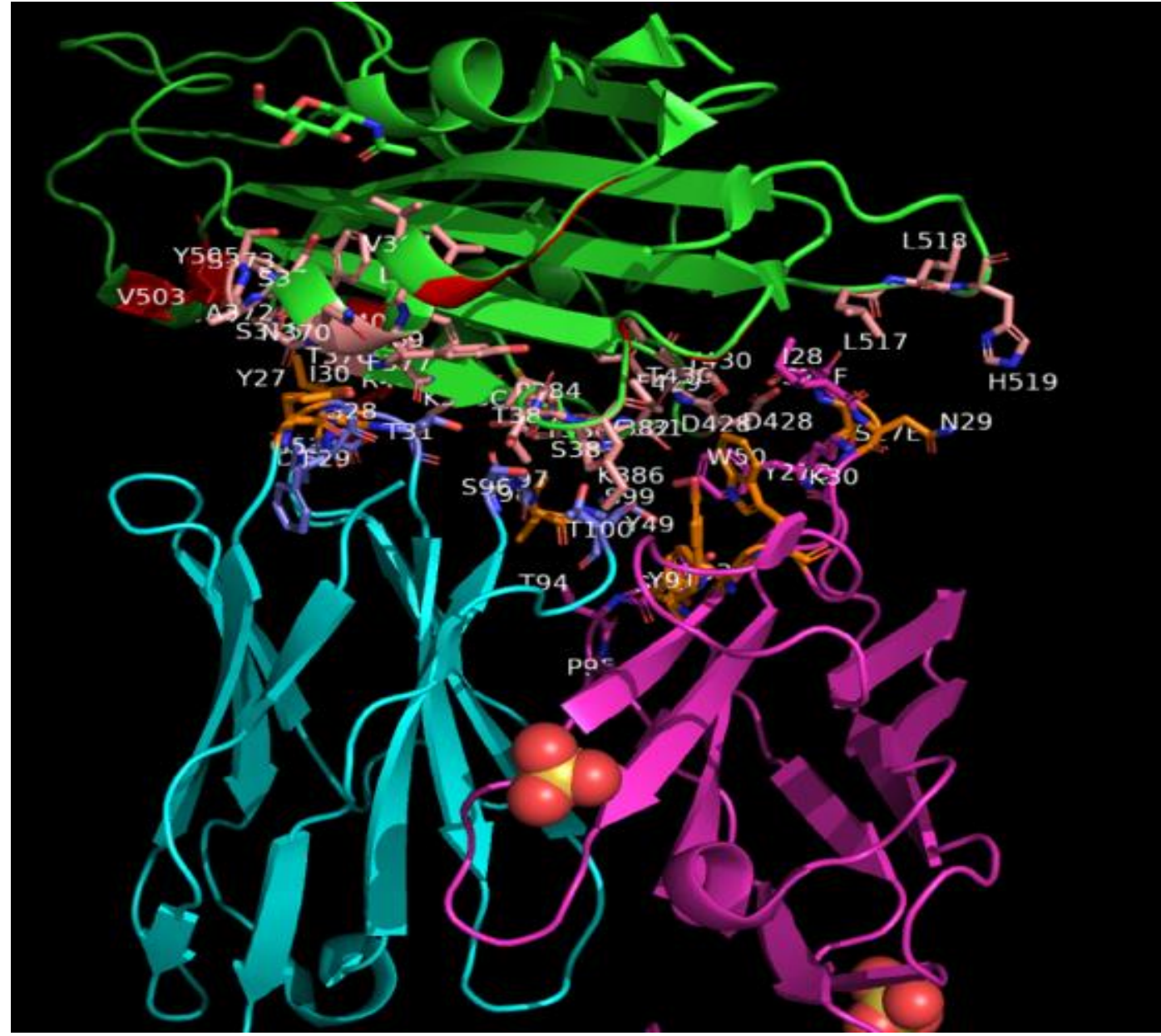
The epitopes for CR3022 and COVA1-16 coincides with the toxin-like epitope 375-390



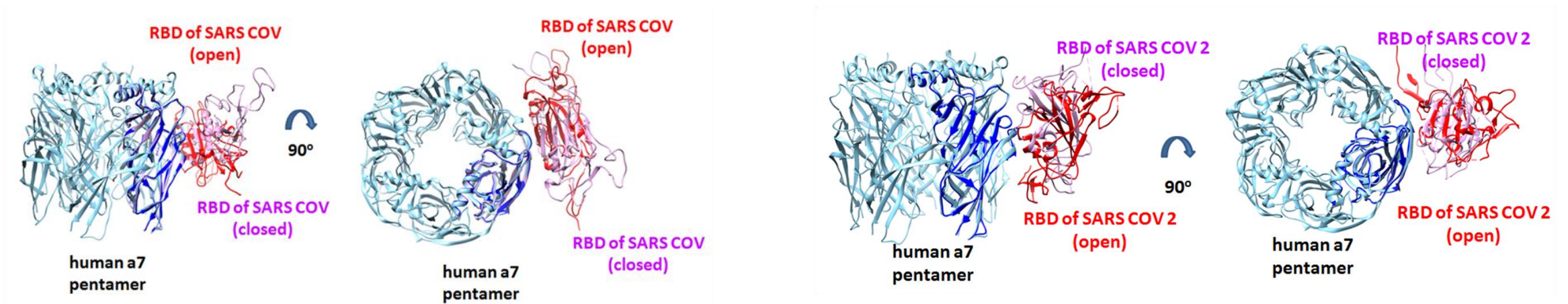
HUMAN ANTIBODIES - MUTANTS



INTERACTION
OF THE MUTANTS
WITH
SARS-COV-2
SPIKE



Similar interaction with SARS-CoV 2003 epidemic



Similar interaction with both SARS-CoV and SARS-CoV-2

Limitations

- Still a hypothesis under investigation
- Other factors could explain the findings (sociodemographic, under-reporting or false reporting of smoking status, no objective assessment of smoking status)
- No clinical proof that nicotinic agonists affect COVID-19 progression – Clinical trials needed

Preliminary results

Clinical trials are on the way with two “cholinergic agonists” mixtures

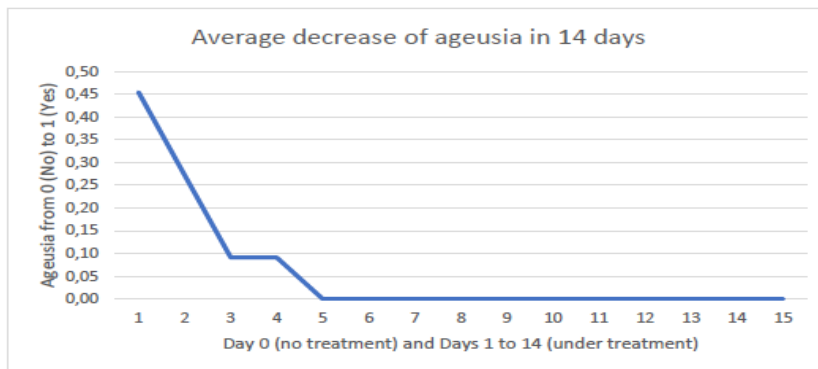
- phytotherapeutic version of the product containing following plants extracts combinations with specific formulations and from special plant varieties: nicotiana sp., Zingiber officinale, Allium sativum, Curcuma longa, and Piper nigrum.
- Synthetic version of the product containing (among other) following molecules and a preferred combination of two or two plus some other of : nornicotine, anabasine, anabaseine, anatabine, cotinine, myosmine, N-formylnicotine, isonicotine, nicotyrine, S-allylcysteine, S-allyl mercaptocysteine, 6-shogaol, 6-gingerol, and curcumin.

AGEUSIA

Day 0 (before starting treatment). Niccovid/Yanavir treatment from Day 1 to Day 14

Initial and final values of ageusia	Day 0	Day 14
Maximum value ageusia	1	0
Minimum value ageusia	0	0
Average value ageusia	0,45	0

Percentage improvement in ageusia	Value in %
Percentage improvement in ageusia at 24 hours	40%
Percentage improvement in ageusia at 48 hours	80%
Percentage improvement in ageusia at 72 hours	80%
Percentage improvement in ageusia at day 14	100%



ANOSMIA

Initial and final values of anosmia	Day 0	Day 14
Maximum value anosmia	1	0
Minimum value anosmia	0	0
Average value anosmia	0,55	0

Percentage improvement in anosmia	Value in %
Percentage improvement anosmia at 24 hours	33%
Percentage improvement anosmia at 48 hours	50%
Percentage improvement anosmia at 72 hours	67%
Percentage improvement anosmia at day 14	100%



Research in order to identify the direct interaction between SPIKE and nAChRs (COLLABORATION: IMPERIAL COLLEGE)



Clinical trials for nicotine and varenicline



Peptide synthesis – Competition experiments (MERCK ISRAEL)



ELISA development – Biomarker characterization



Mouse, Human, Humanized antibody production (WEIZMANN INSTITUTE-ISRAEL)

Conclusions

- Severe COVID-19 is a disease of immune dysregulation and hyper-inflammation (cytokine storm).
- The nicotinic cholinergic system is an immune modulator.
- Smokers appear to be under-represented among hospitalized COVID-19 patients.
- Nicotine is the most plausible candidate for smoking-related effects.
 - Smoking is expected to mask the potential benefits of nicotine.
- Hypothesis
 - Protective effect on nicotinic acetylcholine receptors which may be dysregulated by the virus.
 - Hospitalization results in abrupt cessation of nicotine intake (unless NRTs are administered during hospitalization) → plasma nicotine levels non-detectable within 10-12 hours after hospital admission → unsaturated receptors → possible harm due to abrupt nicotine cessation
- Mechanisms are still under investigation.



THANK YOU