Review: Pharmacology of Ivermectin and Methylene Blue

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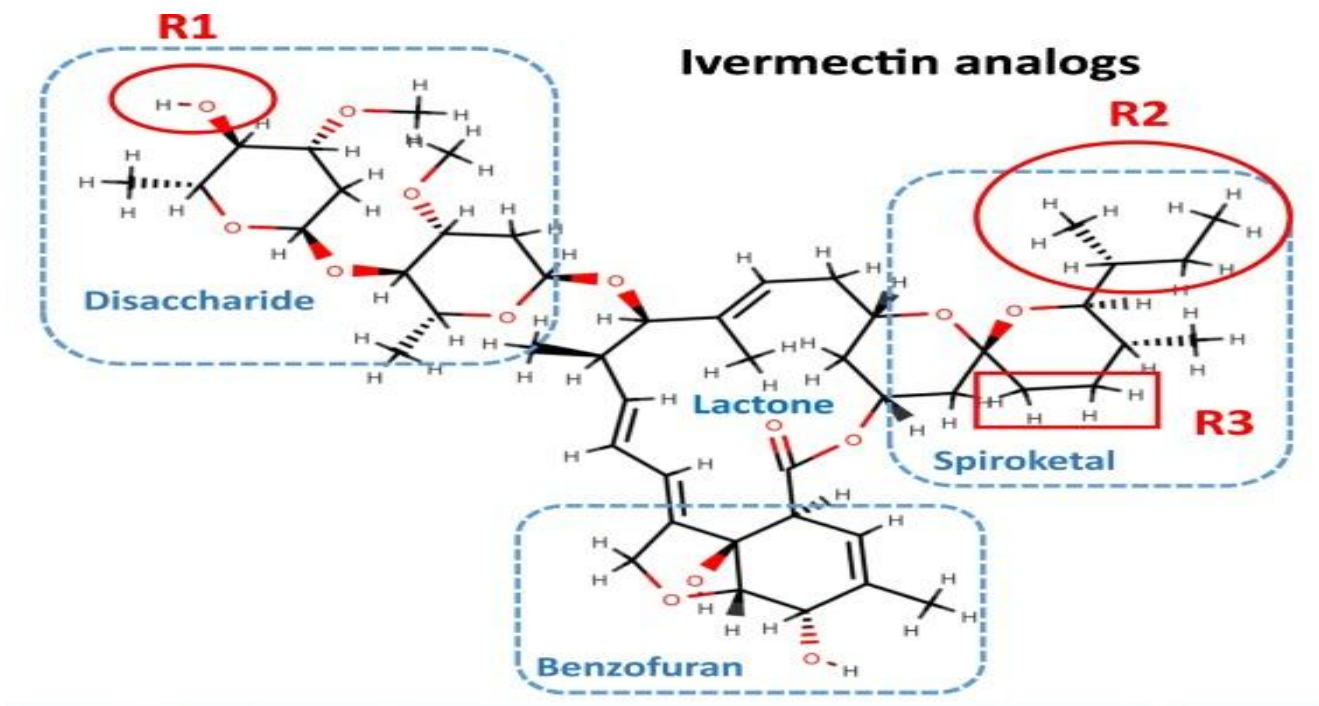
Brief history of ‘Avermectins’

- First isolated ‘Avermectins’ from Japanese Streptomyces bacteria cultures in 1970, Dr. Satoshi Omura and Dr. Wm. Campbell of Merck & Co.
- Anti-helminthic actions discovered around 1975, bacteria named s. Avermitilis, meaning, kills vermis (worms)
- Introduced to market in 1981 as Ivermectin, found to be a broad spectrum anti-parasitic agent
- Ivermectin use extended to world-wide markets for both human, veterinary and animal product uses. Nearly eradicated many pandemic parasitic infections in less developed regions
- Dr. Omura, et.al received the 2015 Nobel Prize in Medicine for work with Ivermectin and parasitic infections
- Since 2015, Ivermectin has been found to have other properties with applicable clinical applications, antiviral, anti-inflammatory

Analogs and structure

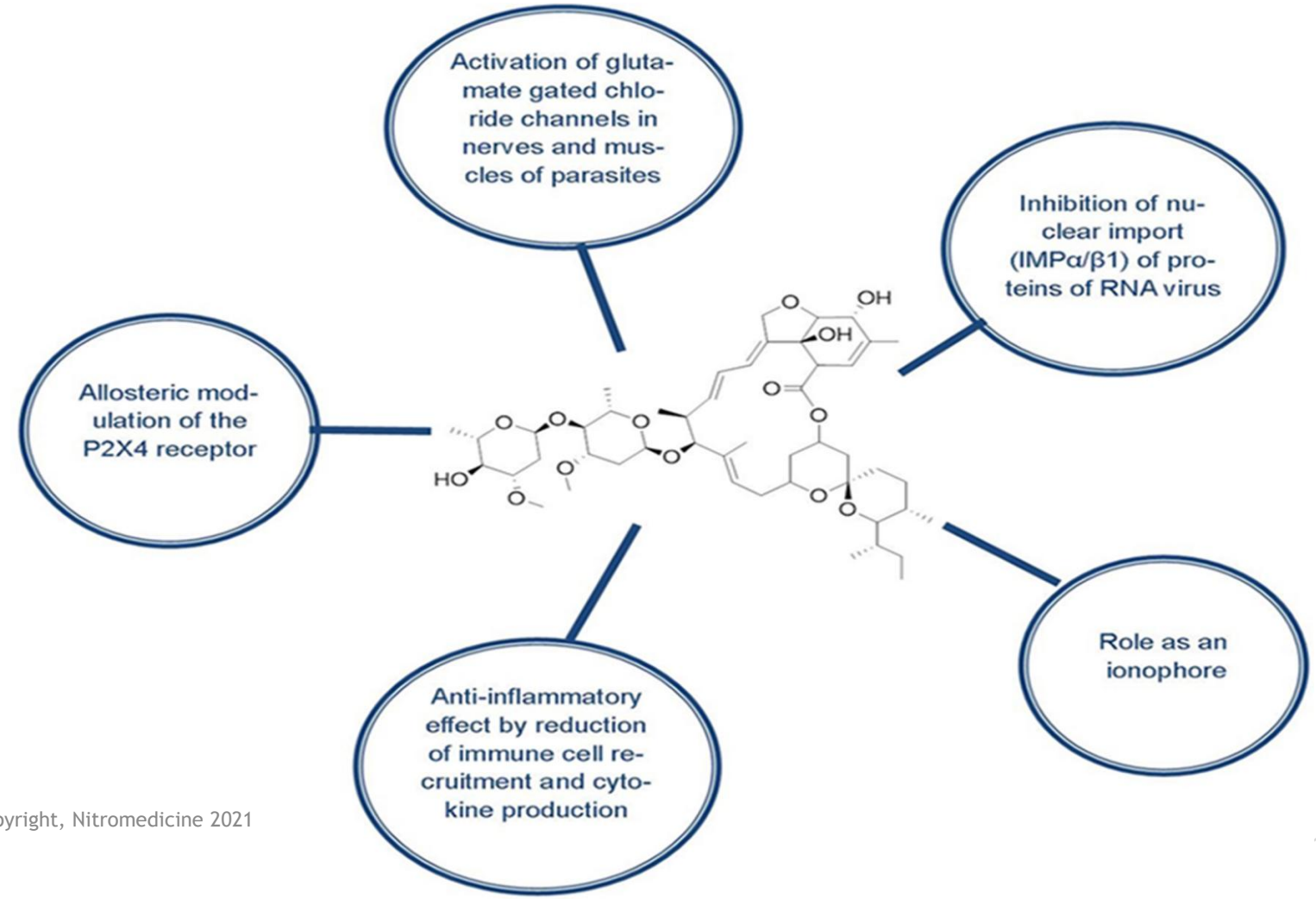


A closer look at Ivermectin

- Ivermectin was originally a mixture of ‘at least 80% 22,23 Dihydroavermectin B1a and up to 20% of the B1b variant, nomenclature is confusing
- FDA product defines Ivermectin as 90% A1b and 10% B1a,
- Stay tuned for other variants, H2B1a, A1a, etc
- Ivermectin is a white, non-hygroscopic powder, melting at 155C, MW=875.1 (large molecule)
- Insoluble in water, freely soluble in ethanol
- PubChem: https://pubchem.ncbi.nlm.nih.gov/compound/ivermectin
- FDA Approved drug component, both Vet and Human, but under different USP monographs and testing standards
- In short, it is a large molecule with several distinct polarized regions that can block ligand-mediated channels and form cross-links between binding sites to disrupt key biochemistry
- Ivermectin acts as an ‘allosteric modulator’ because it changes receptor ‘shape’

Ivermectin Mechanisms of Action

https://link.springer.com/article/10.1007/s43440-020-00195-y/figures/1



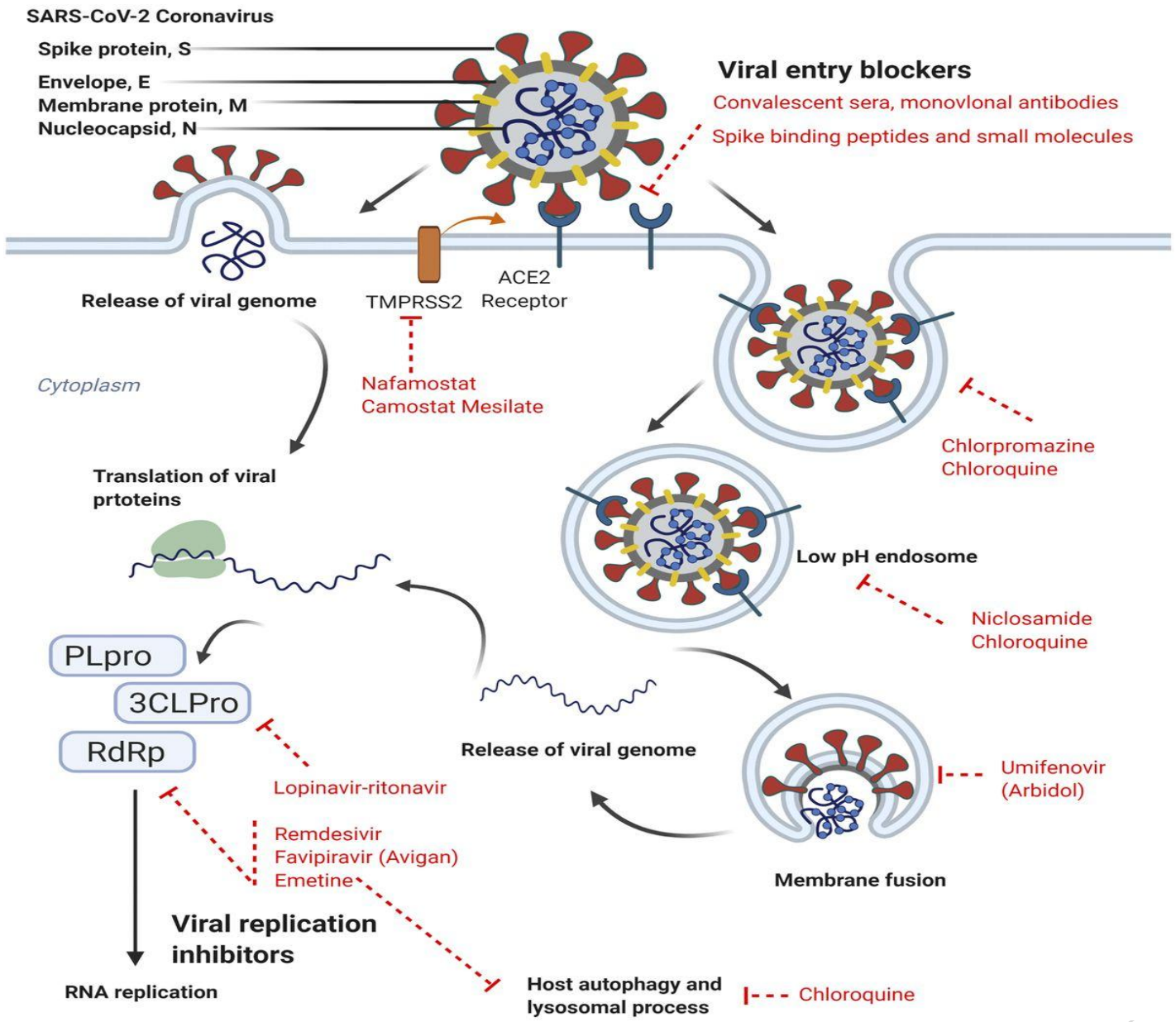
MOA for invertebrates: FDA approved use in humans and animals

- Invertebrate nerve and muscle cells are high in glutamate-gated chloride ion channels. Ivermectin has ‘high affinity/high specificity’ for these channels, essentially blocking them open, leading to hyperpolarization of cell membranes and critical dysfunction
- Other ligand-gated chloride channels are also affected, including GABA.
- Ivermectin affinity for human/mammalian ligand gated chloride channels is LOW, and most are behind BBB
- Ivermectin does not cross BBB in low and moderate doses in healthy individuals
- Many species of invertebrates and most mammals do not have Ivermectin sensitive gated channels or there is poor affinity, thus drugs are selective by species based on receptor affinity

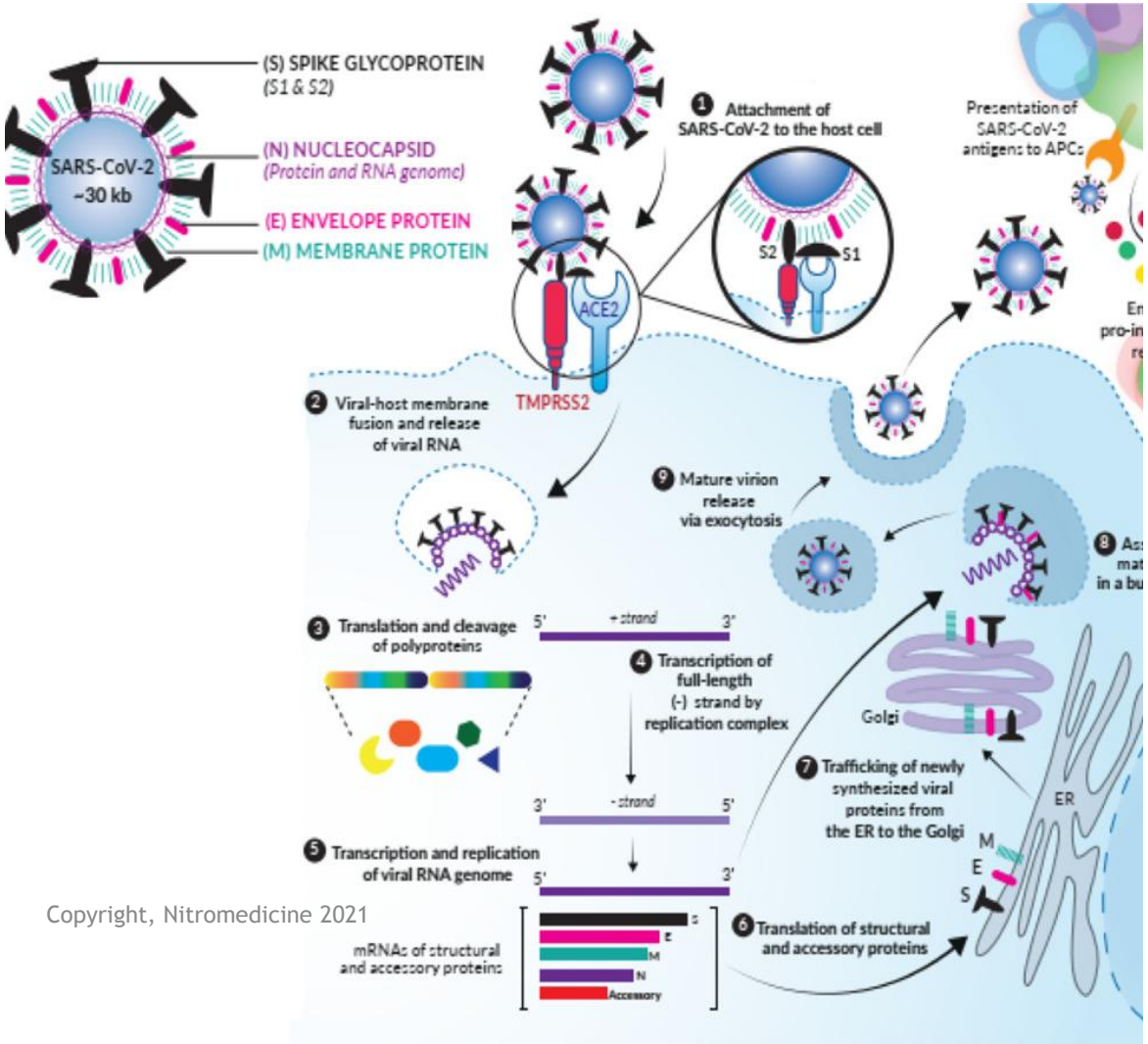
Ivermectin: Multiple broad spectrum anti-viral mechanisms of action

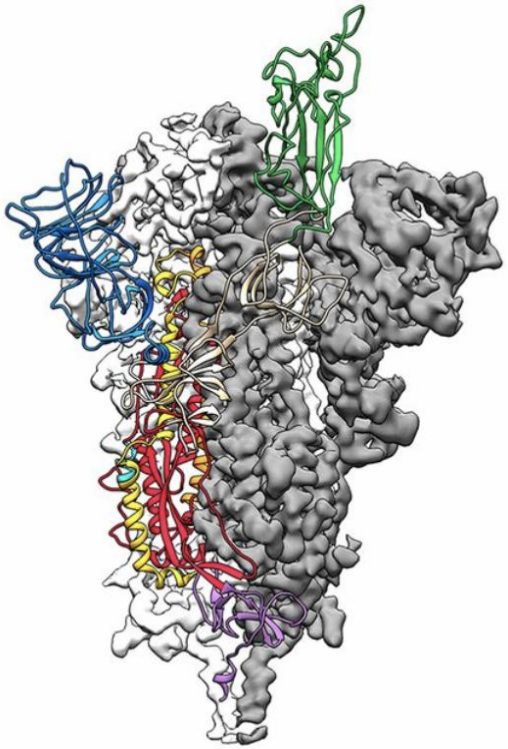
https://www.nature.com/articles/s41429-020-0336-z

1	At Cell Membrane Level: Ivermectin can bind directly to COVID/viral spike proteins complexes, blocking entry by endocytosis at cell membrane
2	At Nuclear Membrane Level: Ivermectin can bind to importin a/b heterodimer, blocking transport at Nuclear Pore Complex
3	Direct inhibition of viral replication at NS3 Helicase in ‘flavoviruses’ 2012


SARS-CoV-2 Coronavirus
Spike protein, S
Envelope, E
Membrane protein, M
Nucleocapsid, N
Viral entry blockers
Convalescent sera, monovlonal antibodies
Spike binding peptides and small molecules
Release of viral genome
TMPRSS2
ACE2
Receptor
Cytoplasm
Nafamostat
Camostat Mesilate
Chlorpromazine
Chloroquine
Translation of viral
prtoteins
Low pH endosome
Niclosamide
Chloroquine
PLpro
3CLPro
RdRp
Release of viral genome
Lopinavir-ritonavir
Umifenovir
(Arbidol)
Remdesivir
Favipiravir (Avigan)
Emetine
Membrane fusion
Viral replication
inhibitors
RNA replication
Host autophagy and
lysosomal process
Chloroquine

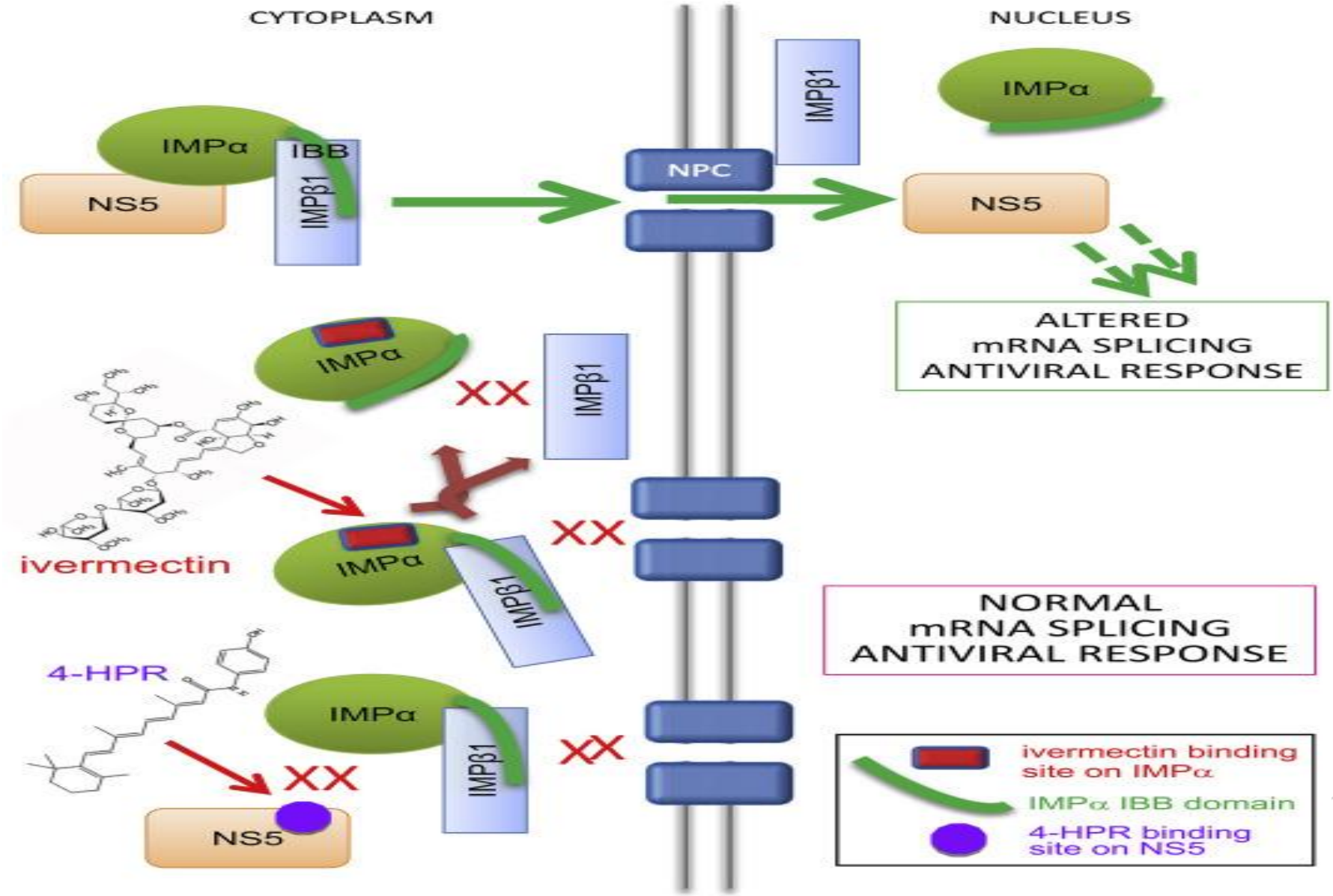
Mechanism of ivermectin blockade of endocytosis via ACE2/TMPRSS2/Furin

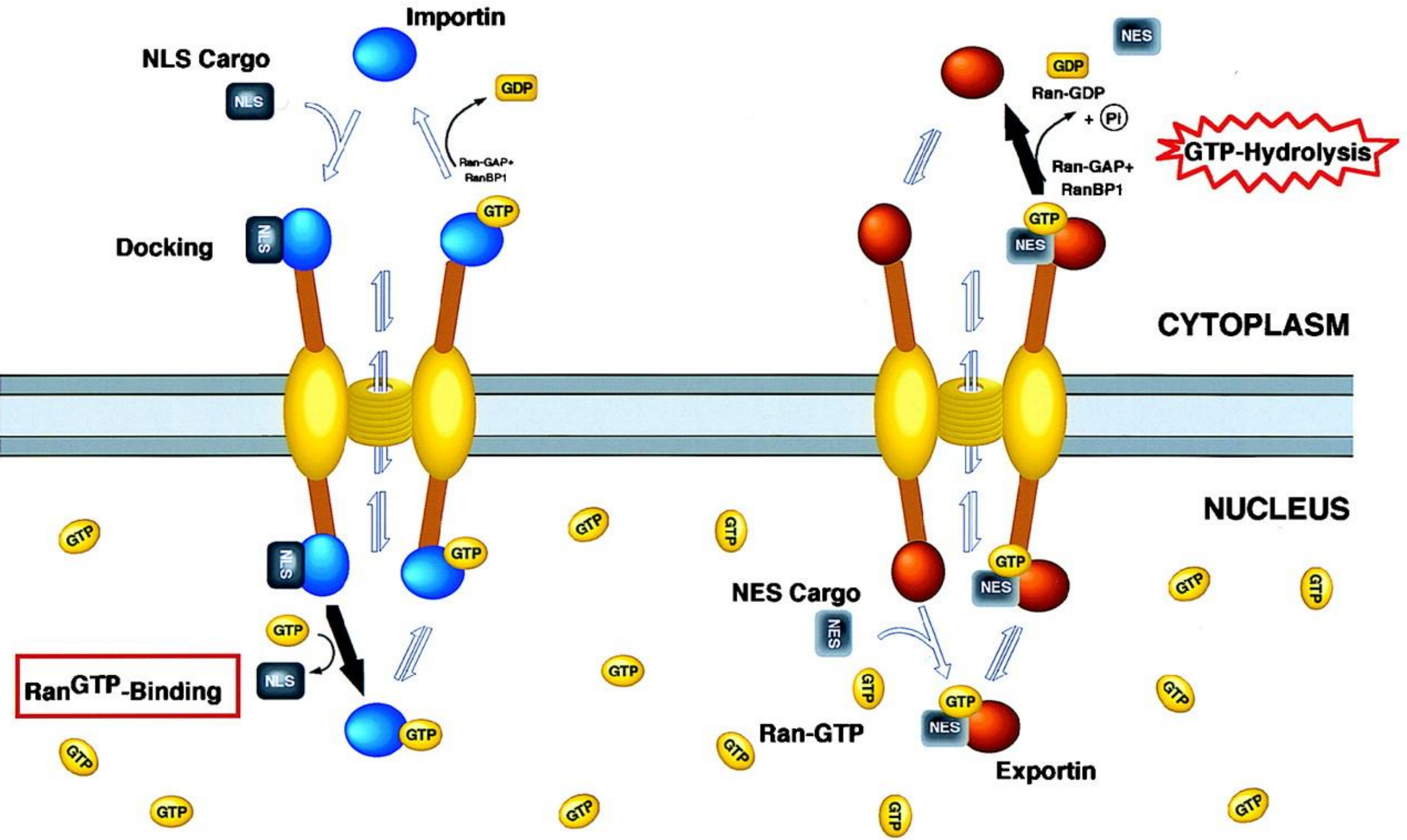




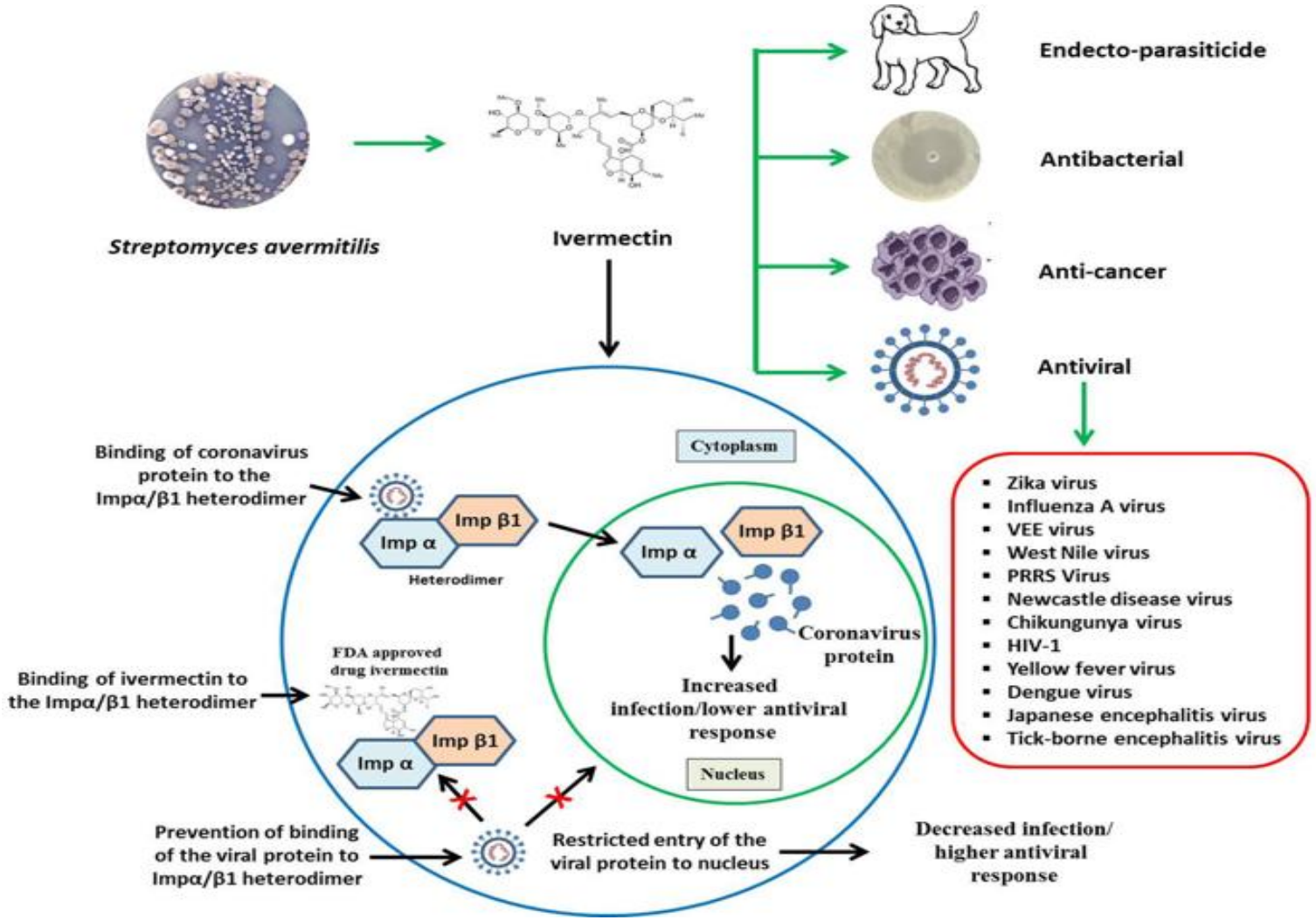
Viral membrane

Nuclear Membrane Blockade via Importin

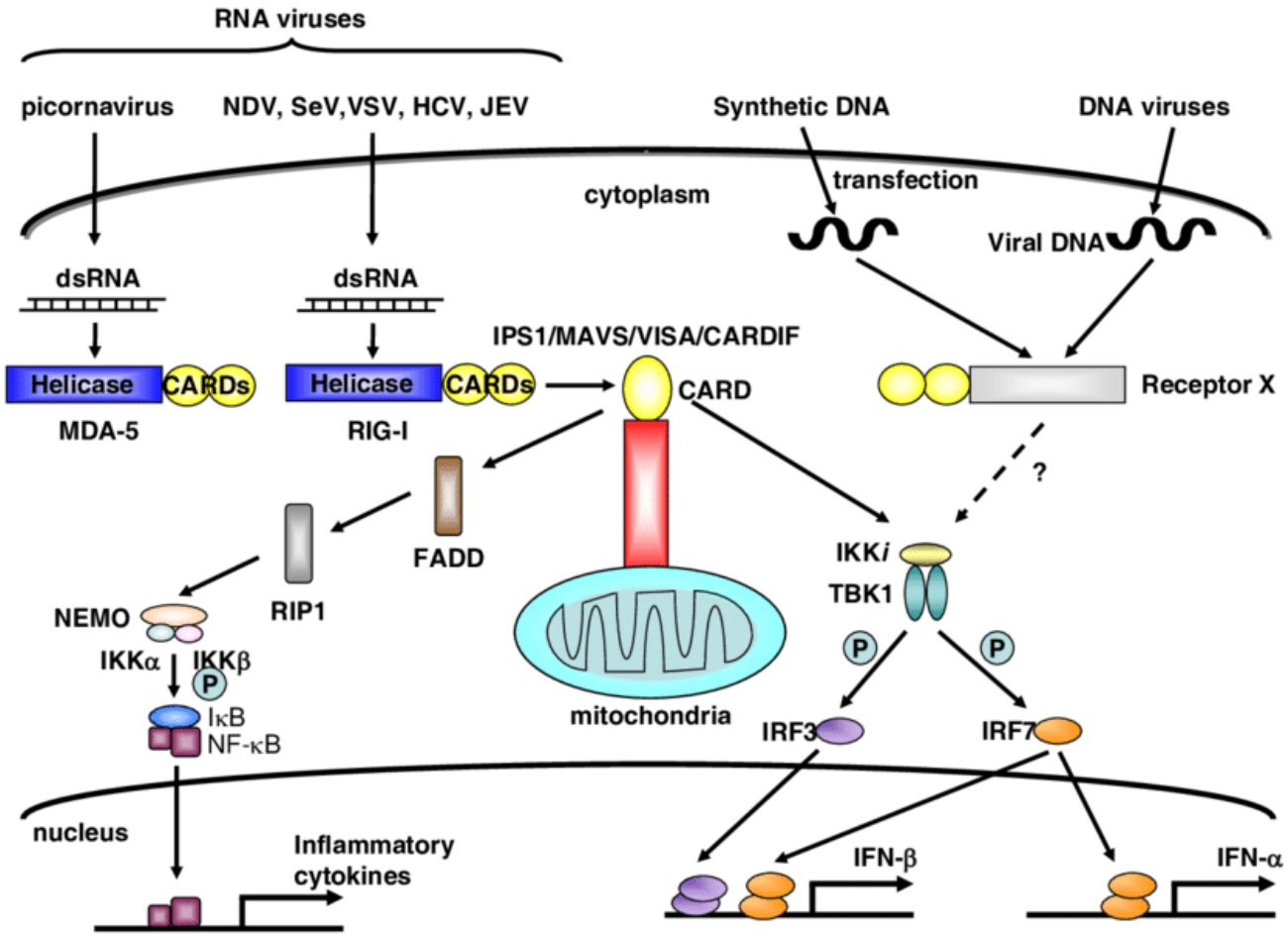



Importin
NLS Cargo
NLS
GDP
Ran-GAP+
RanBP1
Docking
GTP
NES
GDP
Ran-GDP
+ Pi
GTP-Hydrolysis
Ran-GAP+
RanBP1
CYTOPLASM
NUCLEUS
NES Cargo
Ran-GTP
Exportin
RanGTP-Binding

Summary of mechanisms/Ivermectin



Helicase inhibition and signaling

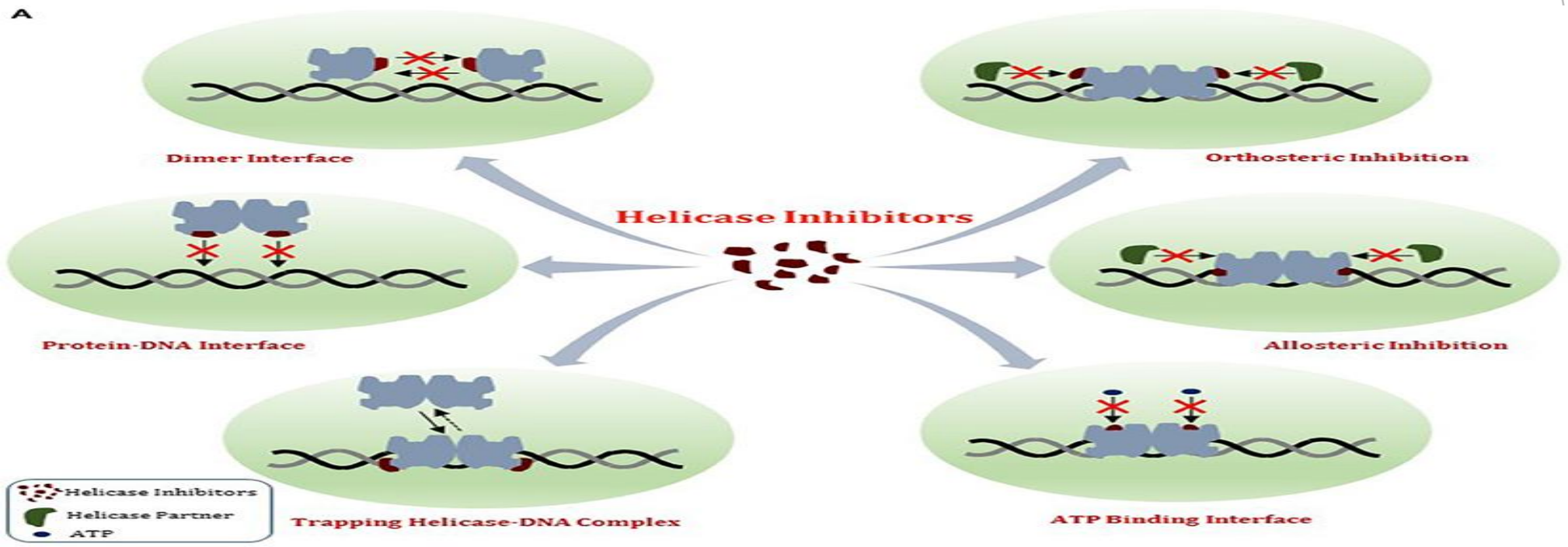


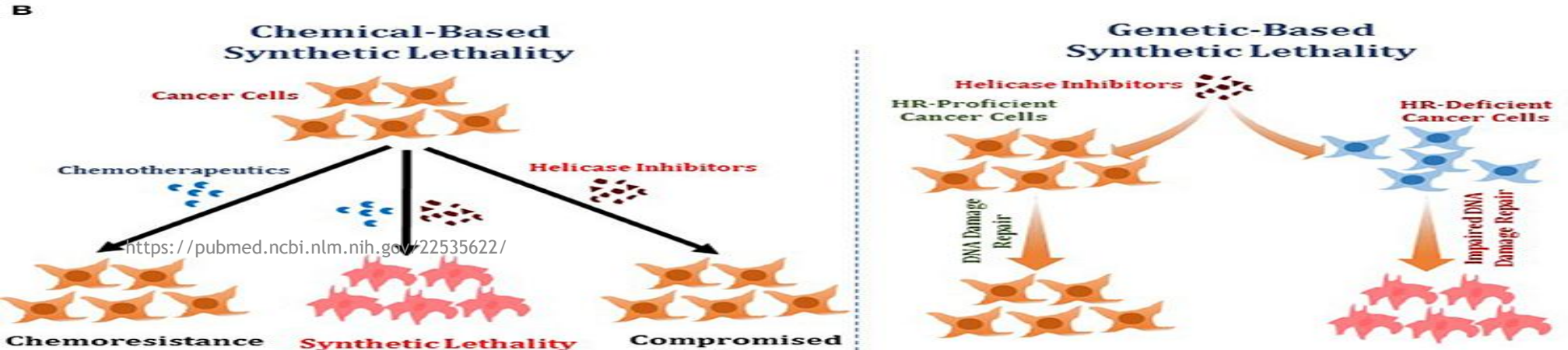
https://www.researchgate.net/figure/Signaling-pathways-of-anti-viral-RNA-helicases_fig1_226009197

Inhibition of viral RNA Transcription: Helicase inhibitors

https://www.frontiersin.org/articles/10.3389/fmolb.2018.00059/full

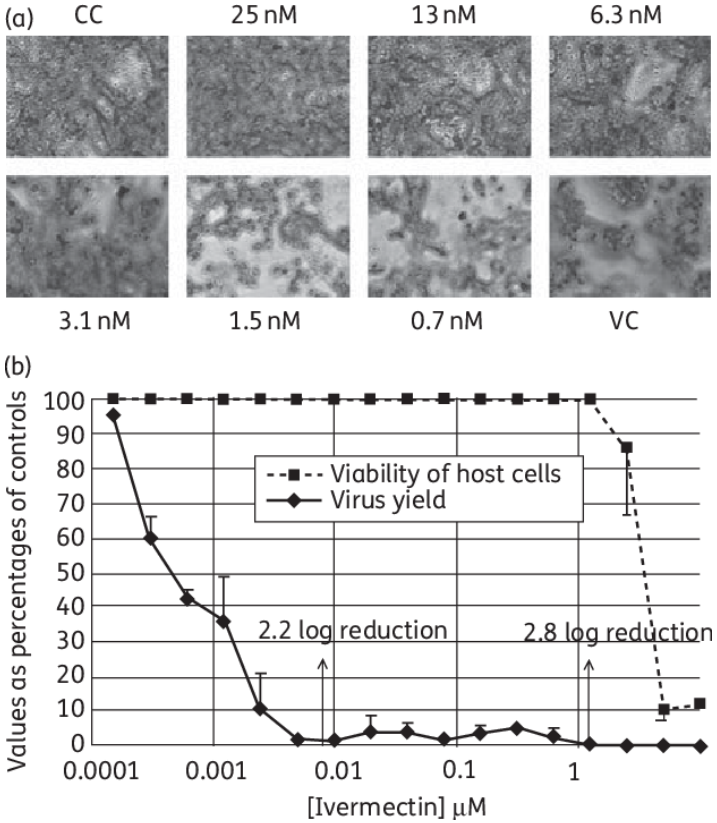
https://pubmed.ncbi.nlm.nih.gov/22535622/





Viral Helicase inhibitor effects

Ivermectin is a potent inhibitor of flavivirus replication, specifically targeting NS3 Helicase activity: https://www.semanticscholar.org/paper/Ivermectin-is-a-potent-inhibitor-of-flavivirus-NS3-Mastrangelo-Pezzullo/0e3ce9e4b36ca8911879e3ef5d413fdc83d05450

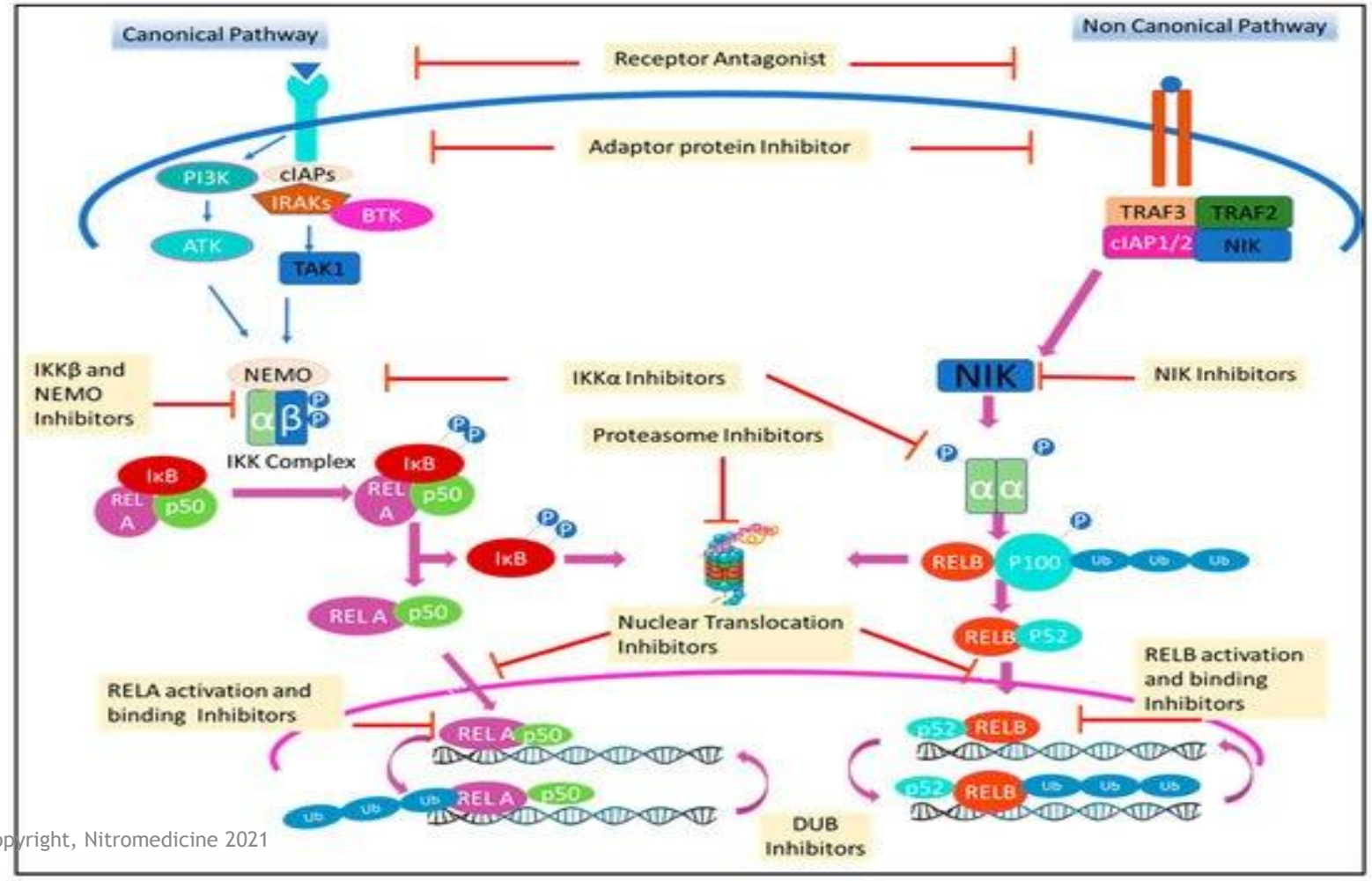


Anti-inflammatory actions need further study

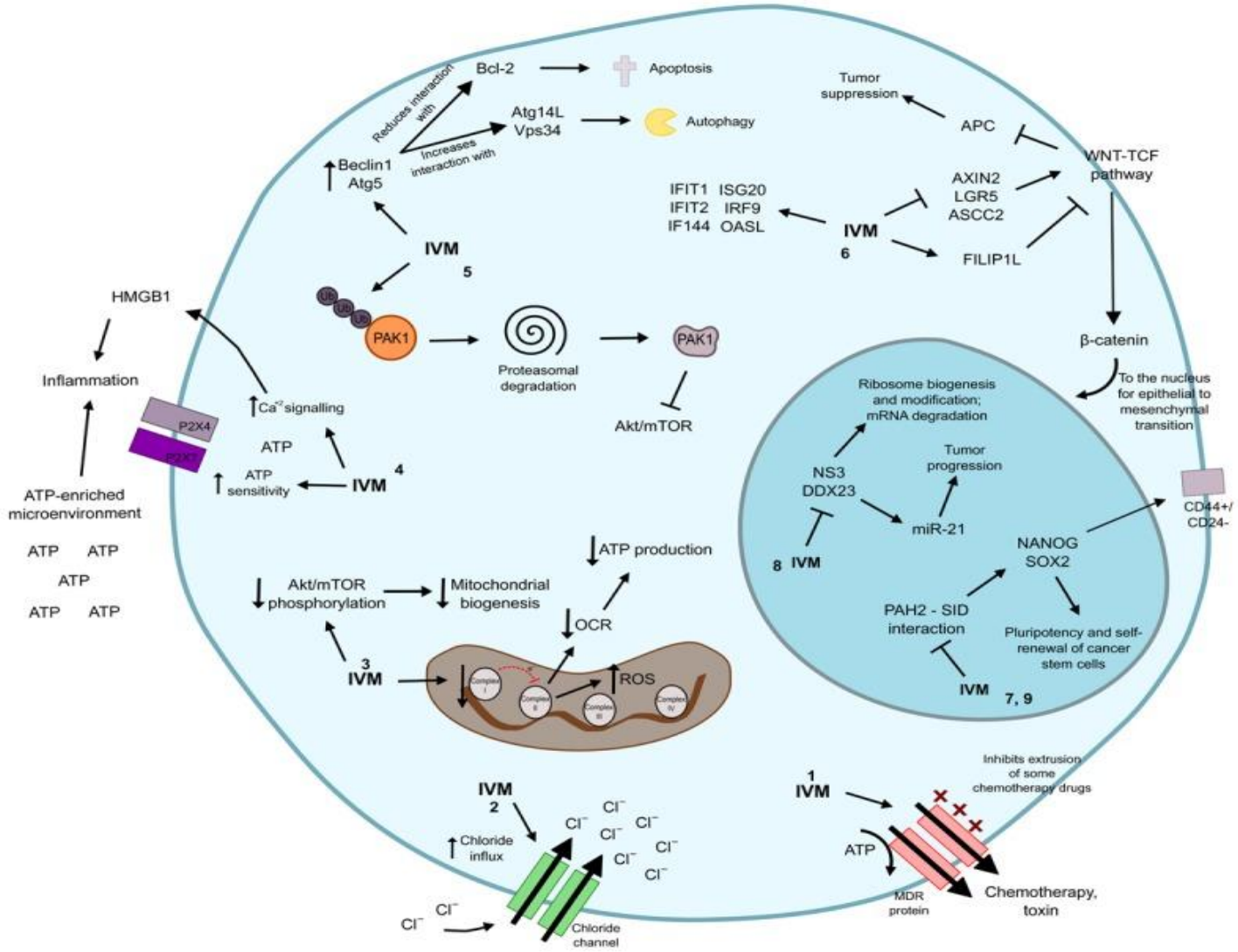
- It has been clinically documented through patient testing that ivermectin has anti-inflammatory effects, but the precise mechanism is not known.
- In vitro studies report inhibition of NF-Kb, and various pro-inflammatory cytokines
- Well recognized anti-inflammatory effects in rosacea, again not exactly defined
- Both Zinc and Ivermectin potentiate P2X4 by allosteric modification (Ligand gated cation channels that respond to ATP and are part complex signaling processes)

NF-Kb Pathway with potential intervention points

https://www.mdpi.com/1422-0067/21/14/5164/htm July 2020



Anti-Cancer actions are being researched



Pharmacokinetics

- Plasma concentrations are proportional to oral dose
- Peak levels occur 4-5 hours after oral dosage
- Less than 1% renal excretion
- 99% metabolized in liver by Cyp 450 1A and 3A4 and excreted in stool, half life is 18 hours. (3A4 inducers/antagonists will influence T1/2)
- Biliary recycling creates a second peak level at 6-12h
- Drug is not water soluble, SL is superior to PO dose in AUC
- Fatty meal effects tablet dosage peaks by 2.5x, thus the vehicle and route of administration matter
- https://europepmc.org/article/pmc/5835698

Safety profile has been excellent

- Ivermectin has been FDA approved for human use for various parasitic infections and rosacea variants
- Available as compounded and FDA approved/manufactured drugs
- Both oral and topicals show very low side effect profiles at approved dosages (0.2mg/kg)
- Oral dosage side effects are generally rare, fatigue (0.9%), GI Upset (1.8%)
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050742s022lbl.pdf)
- Pregnancy Cat C

Potential concerns with overdosage in late COVID-19 infection

- Severe COVID-19 infection and hyper-inflammation (cytokine storm) increases endothelial permeability and may damage BBB to the extent that sufficient ivermectin can pass and create neurologic damage in the same manner as in parasites.
- Normally, ivermectin cannot pass BBB, but in COVID it is more likely
- Inside BBB, humans have similar glutamate gated Cl- channels that can be locked open, thus potentially damaging neurons.
- This is dose-dependent effect

Ivermectin, viruses and COVID-19 Pandemic

- Front-Line COVID-19 Critical Care Alliance
- https://covid19criticalcare.com/
- Very new updates, the data is convincing
- ‘First to discover’ versus ‘Success has many fathers’ Jealousy?
- ‘Drug discoverers’ who miss crucial indication and data are not entitled to claim discoveries they did not make as IP later (Ivermectin, MB, Imiquimod, 5FU, many others)
- https://www.frontiersin.org/articles/10.3389/fphar.2021.643369/abstract

Methylene Blue and Ivermectin?

- Ivermectin and Methylene Blue are two existing FDA approved drugs with long and favorable world-wide safety profiles AND growing evidence of effectiveness for treatment of many various pathogens including bacteria, fungi, viruses and parasites.
- Has there been undue repression of discoveries using existing, already approved drugs?
- False claims (fair) versus ‘protection of the approval process’ (unfair)
- Peer review, off label prescribing, professional judgment, prescribing authority…
- Where is the line in the sand?
- State licensure versus federal ‘approval’
- Patient care TRIAD versus ‘evidence based medicine/FDA approval process for manufacturers to achieve safety and efficacy of treatment

Mehtylene Blue Dosage and Administration

- FDA approved dosage for acute Methemoglobinemia is intended for temporary use at 0.5mg/kg to 4mg/kg. (This is for ACUTE disease for short Tx, not daily)
- Ongoing oral dosage should start much lower, 5mg BID (10mg/day) and may increase to 20mg BID. For viral infection, 5-10mg q8h with PDT
- Single or 'booster' dose before PDT can be added to daily dosages, within limits above
- IV must be slow infusion of 15-30 minutes, no push or bolus
- Do not inject IM or SQ, it will create a locally excessive dose
- DO not use for intrathecal or intraspinal injection

- **Patient must not have G6PD deficiency**

Methylene Blue Bioavailability and Pharmacokinetics

- MB is highly bioavailable following oral dosage
- Half life is about 5.5 hours
- Peak levels after about 30-60 minutes after oral capsule given with 8oz of water, IV Peak levels are very quick, 5 minutes.
- IV dosage may provide higher levels in deeper tissues more rapidly and may be favorable if targeting CNS.
- Daily doses should be much lower than recommended doses for IV treatment of methemoglobinemia.
- **HAL Id: hal-00477926**
- **https://hal.archives-ouvertes.fr/hal-00477926**

Methylene Blue Contraindications

- Pregnancy Category X! Not for use in pregnancy.
- Not for use in GFR<30 without special assistance.
- MAO-I: Caution/Serotonin Syndrome.
- Not for use with SSRI/SNRI or other serotonin, NE or possibly dopamine increasing drugs (antidepressants, bupropion, methylphenidate/Adderall, phenothiazine antipsychotics, etc).
- DO NOT use in patients with G6PD deficiency! Can cause hemolysis.
- Co-Q-10 competes with MB and reduces its effect, so best not to use both but not harmful.
- NEVER give a full systemic dose by IM or SQ injection.
- NO BOLUS or IV PUSH, only slow infusion in D5W or NS over 30 minutes typically.
- First sign of excessive dosage is typically nausea, dizziness, sweating.

My Recommendations

- For non-vaccinated patients, use Ivermectin once weekly as preventative therapy, along with appropriate nutritional and nutraceutical intervention (Vit D, Quercetin, Zinc, Vit C, etc) plus Methylene Blue 5-10mg BID as appropriate to the patient
- We don't want to use MB or Ivermectin after vaccination
- After 3-4 months, it may be ok to use prevention regimen again for future strains or other viruses
- If a non-vaccinated patient tests positive, consider Ivermectin at a higher dose regimen for 5 days (0.2mg/kg/day for 5 days), and Methylene Blue 1mg/ml oral rinse with PDT every 8 hours.
- MB has both intrinsic and phototherapy antiviral properties that are documented in literature
- Review the FLCCC website weekly for updates

Important Toxicity Notes from FDA!

- Methylene Blue may interfere with pulse oximeter function causing it to read artificially low
- **Even pharmaceutical (USP) grade methylene blue may contain impurities such as arsenic, aluminum, cadmium, mercury, and lead.** At higher doses, some researchers have warned of the danger of these contaminants accumulating in the patient's tissues
- **Industrial-grade and chemical-grade MB sold as a dye or stain can consist of more than 8% or 11% of various contaminants** (NTP, 2008, Sigma Chemical Co, St. Louis, MO) and **should not be administered to humans or animals**
- For example, **commercial chemical suppliers routinely warn that their non-USP MB products are of a chemical grade not suitable for use in living applications**

Message from FDA regarding Vet grade ivermectin

- **Q: Should I take ivermectin to prevent or treat COVID-19?**
- A: No. While there are approved uses for ivermectin in people and animals, it is not approved for the prevention or treatment of COVID-19. **You should not take any medicine to treat or prevent COVID-19 unless it has been prescribed to you by your health care provider and acquired from a legitimate source.**
- **Q: Is there any danger to humans taking ivermectin?**
- A: There are approved uses for ivermectin in people and animals but it is not approved for the prevention or treatment of COVID-19. **You should not take any medicine to treat or prevent COVID-19 unless it has been prescribed to you by your health care provider and acquired from a legitimate source.**