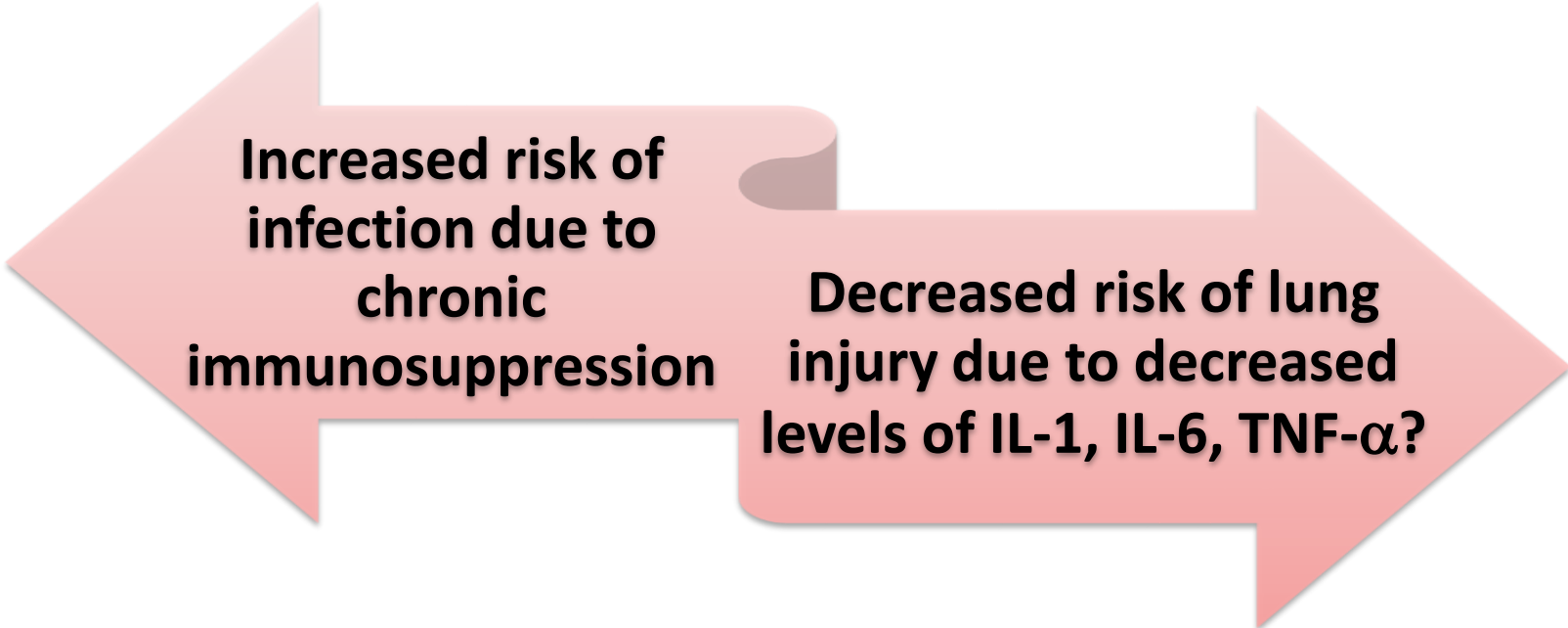


به نام خدا

Adjusting Immunosuppressive Regimen and Drugs Interactions In Kidney Transplant Patients with COVID-19

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SOT Patients vs Other Patients with COVID-19



**Increased risk of
infection due to
chronic
immunosuppression**

The diagram consists of two large, light-red arrows pointing in opposite directions. The left arrow points left and contains the text 'Increased risk of infection due to chronic immunosuppression'. The right arrow points right and contains the text 'Decreased risk of lung injury due to decreased levels of IL-1, IL-6, TNF-α?'. The two arrows meet in the center, creating a symmetrical, hourglass-like shape.

**Decreased risk of lung
injury due to decreased
levels of IL-1, IL-6, TNF- α ?**

Mortality with COVID-19

- 18-28% in hospital mortality among SOT patients
- 3-7% in hospital mortality among general population with COVID-19

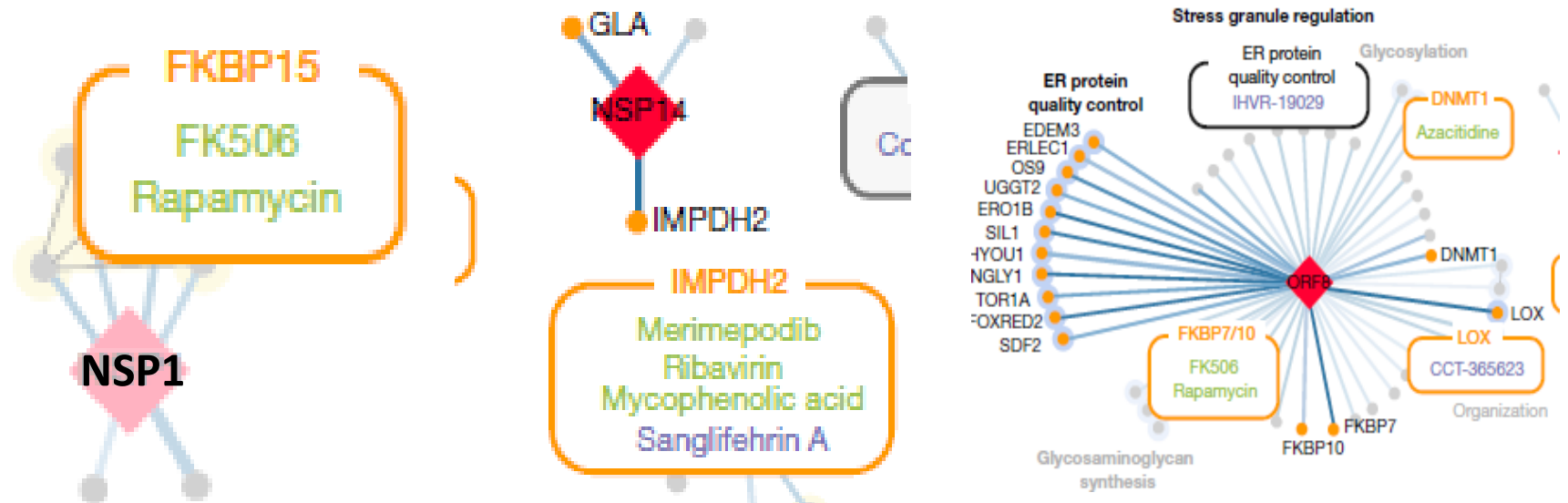
Treatment of COVID-19 Among SOT Patients

- SOT patients with COVID-19 are usually treated as general population.

Principals of Adjusting Immunosuppression

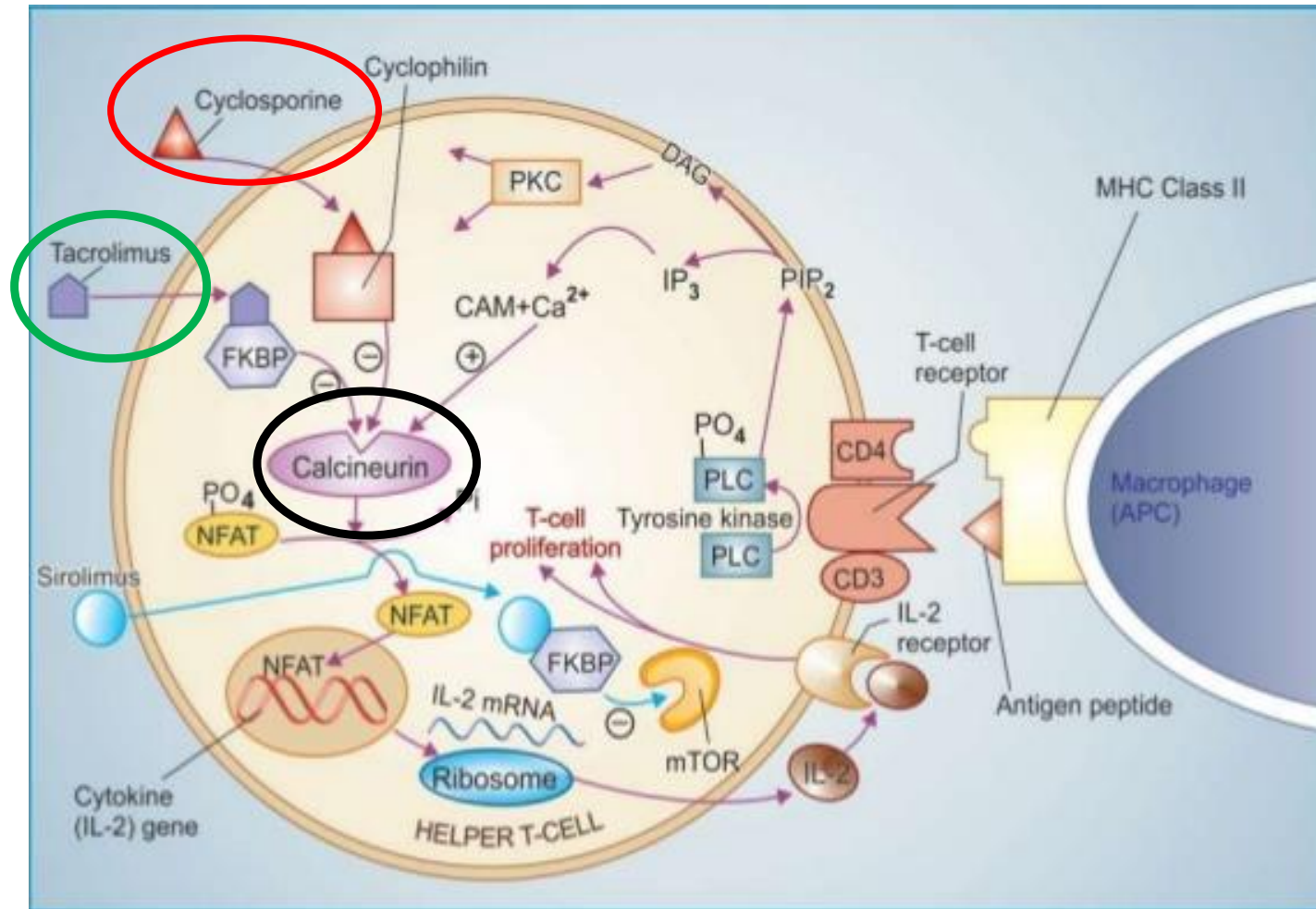
- Antiviral effect
- Immunosuppression Intensity
- ADRs in common with features of COVID-19 (AKI; ↑transaminases; lymphopenia; pneumonitis)

Repurposing of Available Drugs to Treat COVID-19

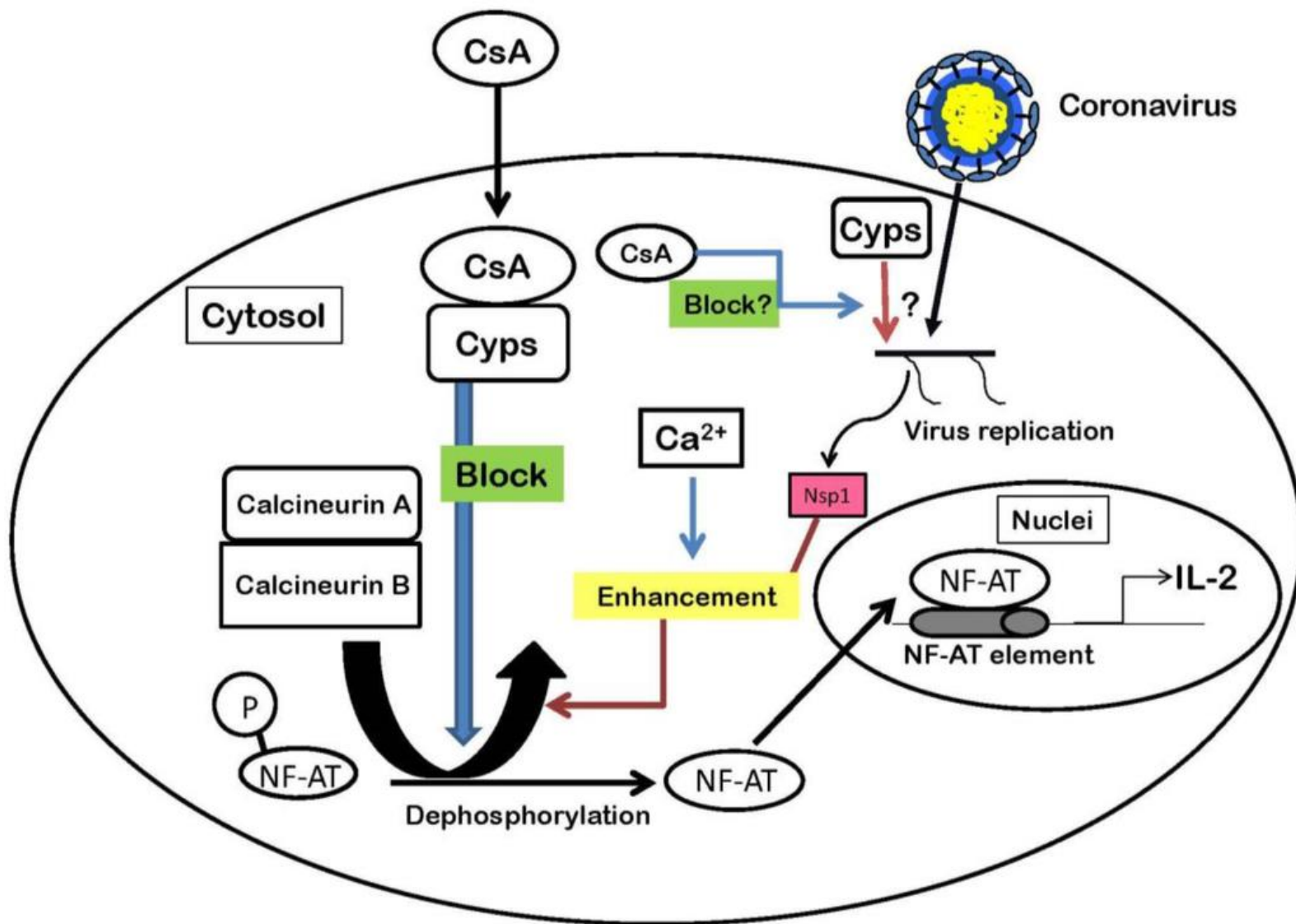


SARS-CoV-2 protein interpretation map reveals targets for drug repurposing. Nature. July 2020.

CNIs



- Cyclosporine binds to an intracellular protein 'Cyclophilin' and this complex inhibits Ca²⁺-Calmodulin (Ca²⁺-CAM) activated phosphatase 'Calcineurin'.



CNIs and COVID-19

- Immunophilins (cyclophilins and FKBP) are cellular interaction partners of some viral non-structural proteins (Nsp1)
- Peptidyl-prolyl isomerase (PPlase) domains facilitating protein folding need for viral replication
- Inhibition of PPlase activity prevents correct folding of viral proteins indispensable for viral replication. (shown first for HIV-1 and HCV and then for some coronaviruses)

1. Ma-Lauer Y, et al. Antiviral Research. 2020. doi: 10.1016/j.antiviral.2019.104620;

2. Pfefferle S, Schöpf J, Kögl M, et al. The SARS-Coronavirus-host interactome: Identification of cyclophilins as target for pan-Coronavirus inhibitors. *PLoS Pathog.* 2011;7(10). doi:10.1371/journal.ppat.1002331

CNIs Clinical Report of 29 Kidney Transplant Recipients with COVID-19 From Spain

- Cellcept and mTORIs were stopped in all patients.

First group (n=6)

Reduced in CNI dose

Mortality

50%

Second group (n=23)

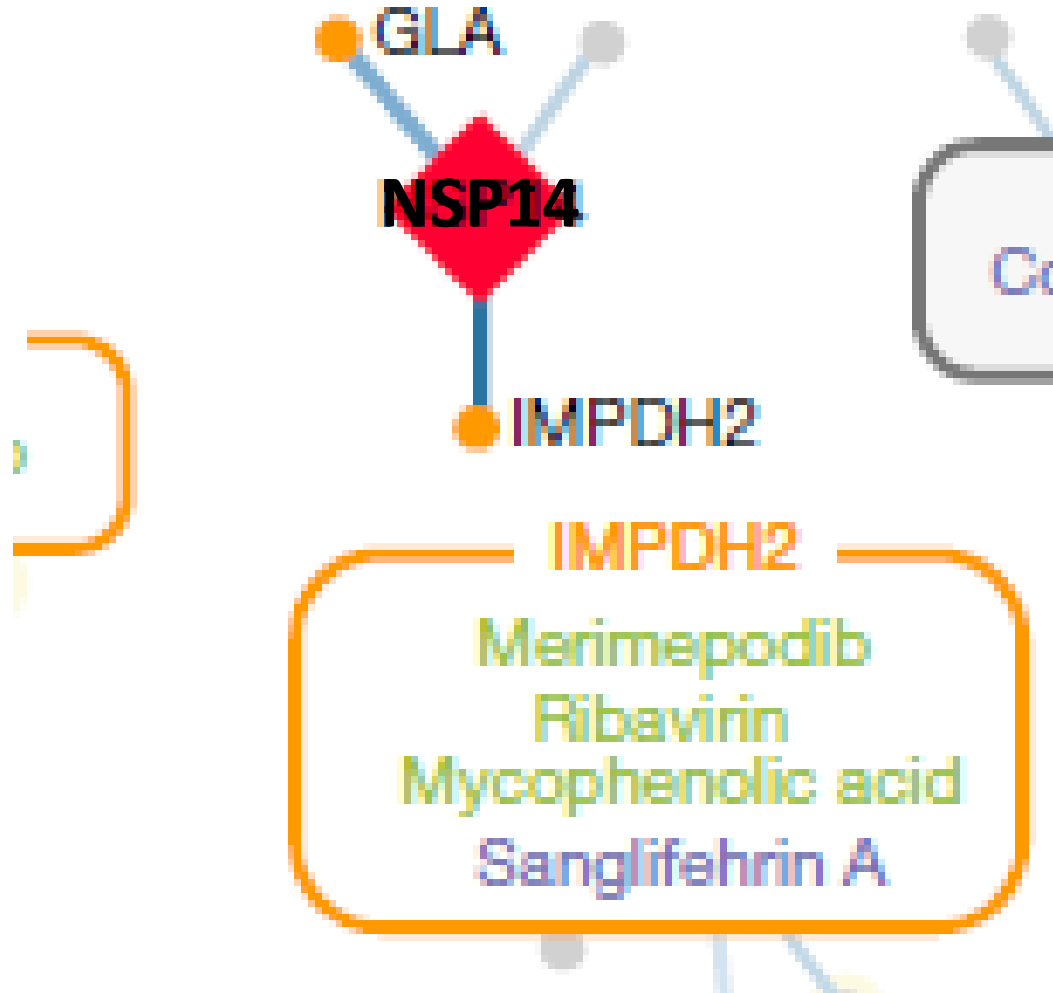
Continued usual CsA dose or
switched from Tac to CsA (n=15) with
[CsA]= 50-100 ng/ml

Mortality

12% (P= 0.047)

No rejection rate

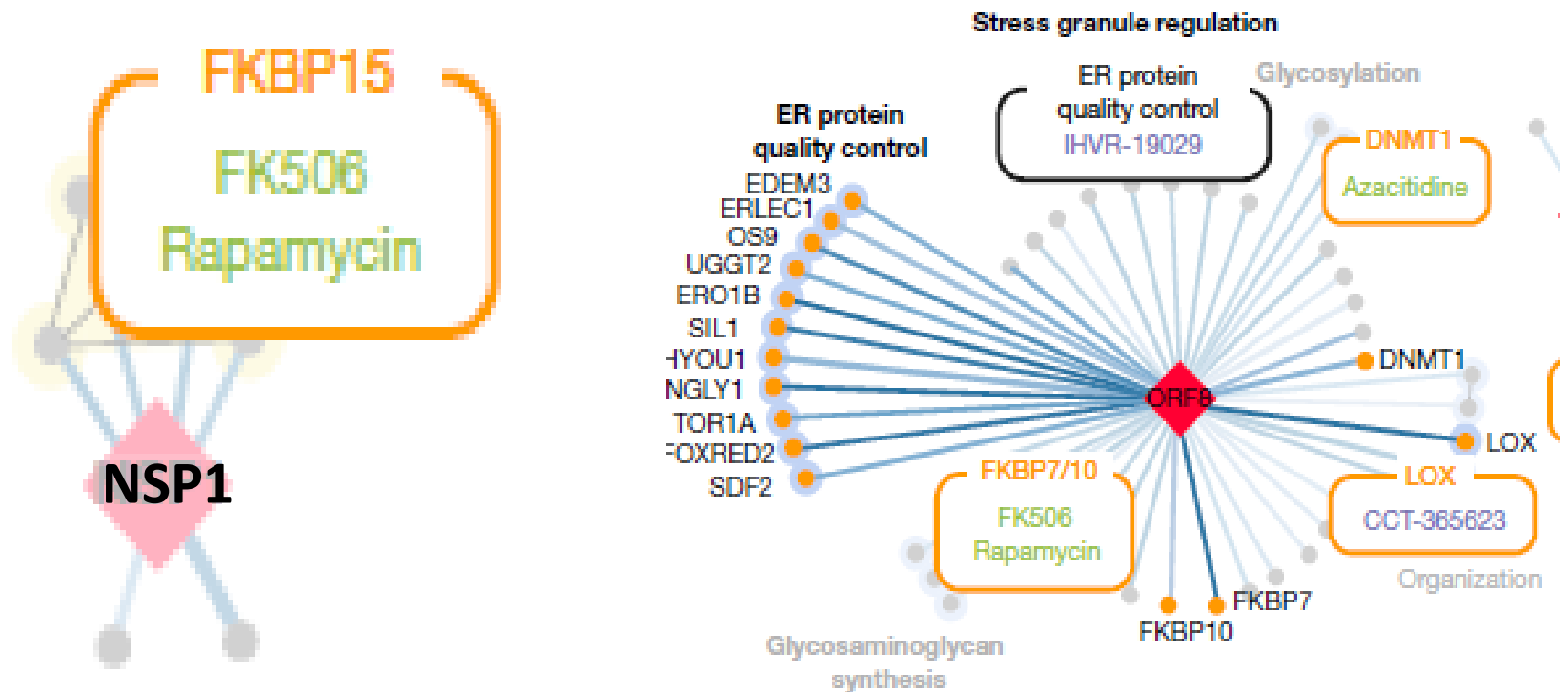
Mycophenolate



Mycophenolate

- Conflicting results regarding antiviral effects of Mycophenolate
- Animal data showed worse outcome when mycophenolate was administered against some members of coronavirus family.
- Mycophenolate has adverse hematologic effects (lymphopenia and thrombocytopenia) that may exacerbate hematologic complications of COVID-19.

mTORIs



SARS-CoV-2 protein interpretation map reveals targets for drug repurposing. Nature. July 2020.

mTORIs

- mTORIs have some antiviral effects (against CMV and BK virus).
- Experimental data suggest mTORIs may have some biologic activities against SARS-CoV-2.
- In vivo, Rapamycin did not decrease HCoV-229E replication.
- Common features with COVID-19 (leukopenia, thrombocytopenia, pneumonitis).

Conti P, et al. Induction of pro-inflammatory cytokines(IL-1 and IL-6) and lung inflammation by coronavirus-19 (CoV-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34: 327-31.

Ma-Lauer Y, et al. Antiviral Research. 2020.

Dashti-Khavidaki S, et al. Expert Opinion on Pharmacotherapy. 2020.

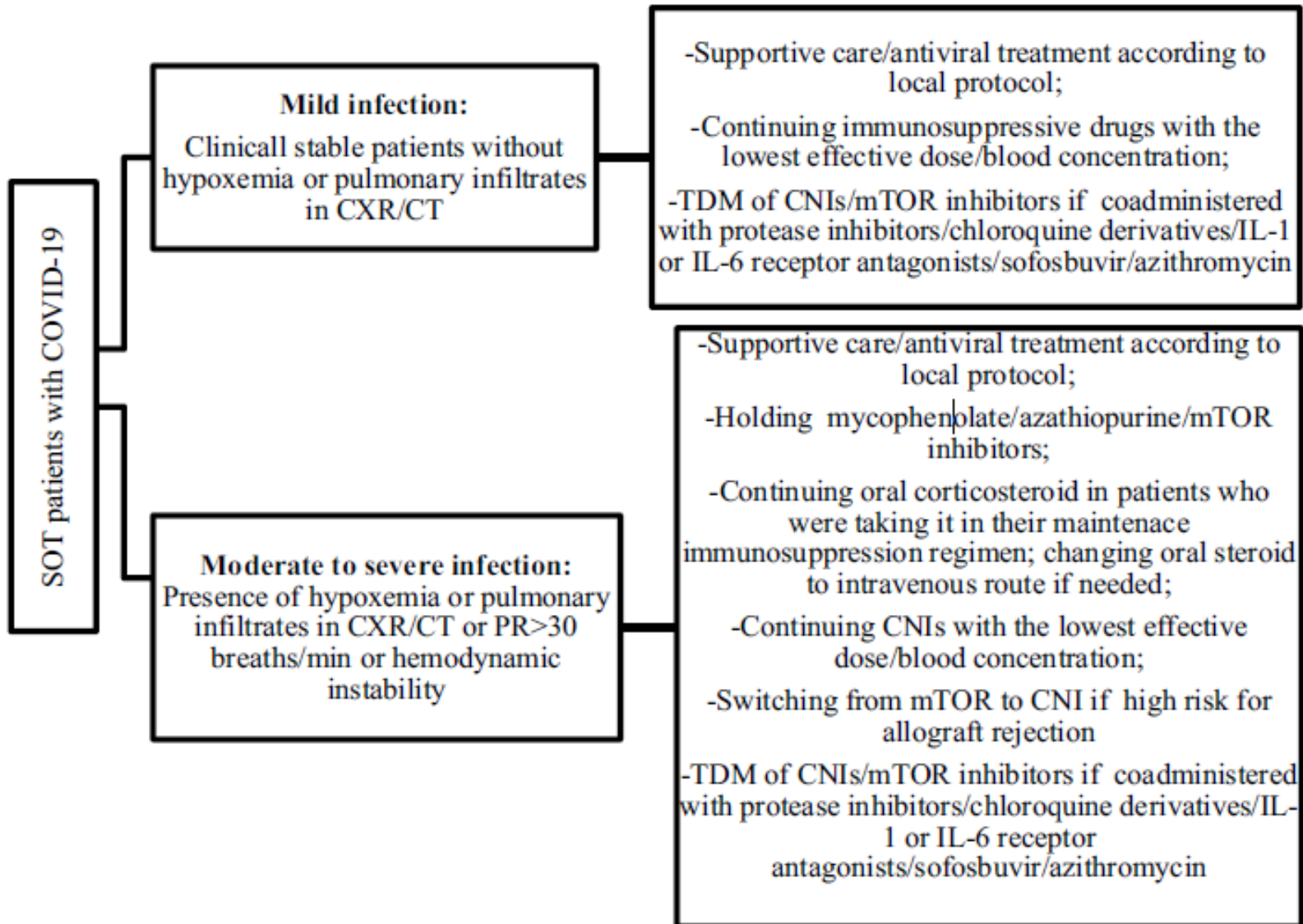
Corticosteroids

- Conflicting results on viral and bacterial pneumonia
- Steroid in those with ARDS or septic shock is suggested.
- Prolongation of viral shedding phase
- Recovery Trial proposed Dexamethasone in patients with severe COVID-19.
- Abrupt cessation of maintenance corticosteroids in infection phase induces risk of adrenal insufficiency.

T-lymphocyte Depleting Agents

- Thymoglobulin, Alemtuzumab
- Their use as induction therapy or treatment of acute rejection should be minimized.

Suggested Approach



Mechanisms of Drug Interactions

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graph TD; A[Mechanisms of Drug Interactions] --> B[Pharmacokinetic]; A --> C[Pharmacodynamic]; A --> D[Additive Toxicity];
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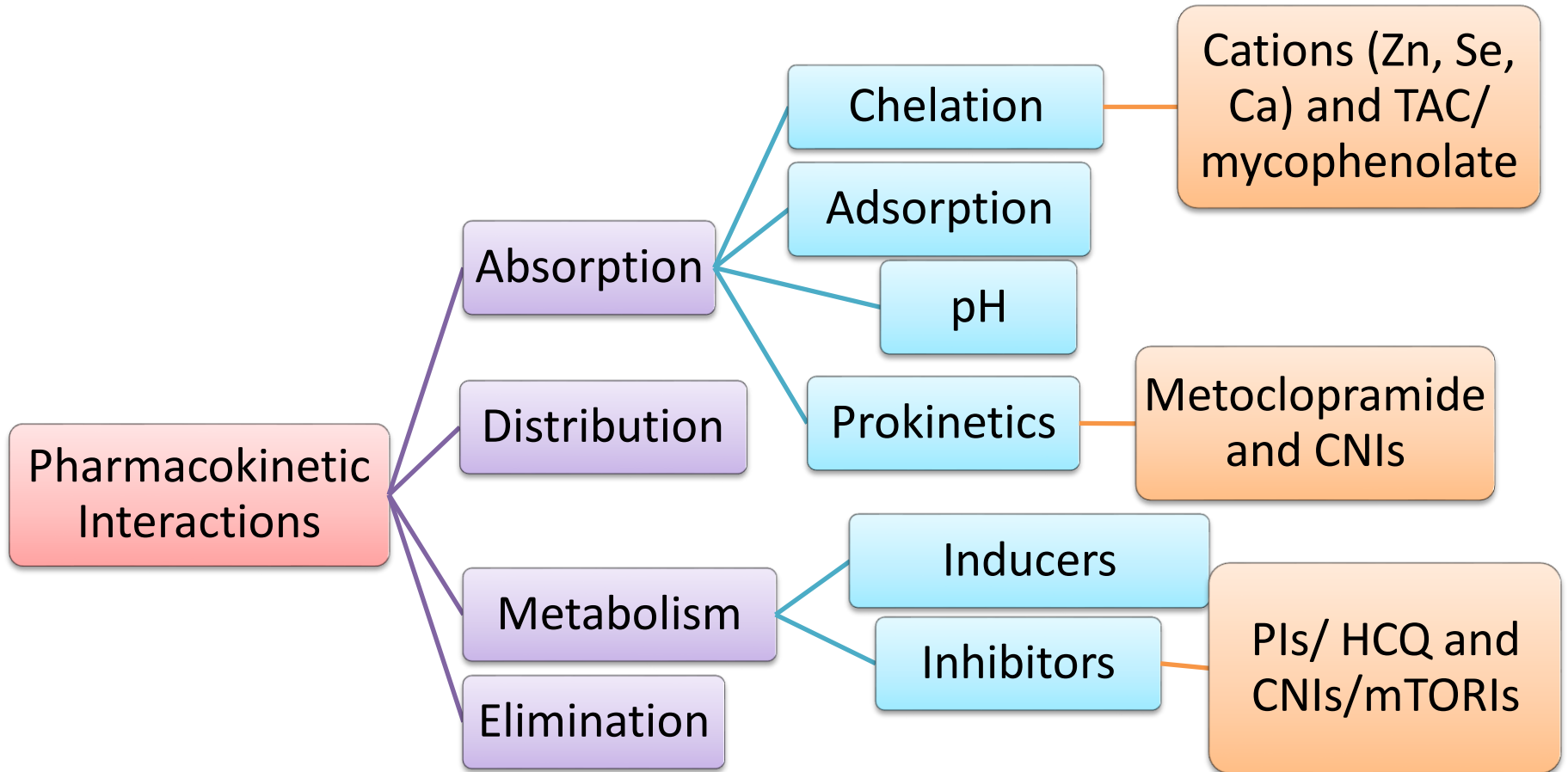
Pharmacokinetic

Pharmacodynamic

Additive Toxicity

Interactions happen between drugs and

- **Other drugs**
- **Disease**
- **Food**
- **Supplements (minerals, vitamins, herbal agents)**
- **Laboratory tests**



Protease inhibitors (PIs)

- Strong 3A4/5 inhibitors especially pharmacokinetic enhanced combinations
- They increase AUC of CNIs (CsA, TAC), mTORIs (SIR, EVR) and also mycophenolate and prednisolone
- This interaction usually **starts one to two days after** the start of PIs and reaches a maximum after a few days and **lasts for several days after PI cessation.**
- TDM of CNIs and mTORIs are recommended.

HCQ

- Inhibits CYP 3A4/5

Management of Interactions with PIs

- CsA dose should be reduced to 5-20% of baseline daily dose (especially if PI and HCQ are administered in combination).
- 0.5-1mg per week TAC would be sufficient to maintain TAC trough blood level between 6-8ng/mL in combination with PIs.
- mTORIs is best to be avoided in combination with PIs.

Our Clinical Experiences

PIs+HCQ and TAC Interaction

- A 41y/o kidney transplant patient
- He had TAC C0=6.6ng/ml with TAC maintenance dose of 2-1mg before COVID-19
- atazanavir/rit+ HCQ was administered from 99/1/17 to 99/1/22.
- TAC was held from 99/1/17 to 99/1/24 i.e. 2days after atazanavir/rit and HCQ cessation and then started with reduced dose of 1mg BD
- TAC Co on 99/1/27 was reported >60ng/ml.
- TAC was held
- TAC C0 on 30/1/99 =14.6
- Conclusion: long lasting interaction

Our Clinical Experiences

PIs+HCQ and CsA Interaction

- A kidney transplant patient with COVID-19
- His CsA maintenance dose at home was 100-75mg
- CsA dose was reduced to 50mg BD with the initiation of atazanavir/rit+HCQ
- After 4 doses of atazanavir/rit, CsA C₀=444.2ng/ml
- 2 days after cessation of atazanavir/rit and 1day holding CsA: C₀=206.9ng/ml

Our Clinical Experiences

PIs+HCQ and SIR Interaction

- A kidney transplant patient with COVID-19
- His SIR maintenance dose at home 2mg daily without blood level during past weeks
- atazanavir/rit was started 98/12/28
- SIR C0=84ng/ml on 99/1/4 and C0=100ng/ml on 99/1/5

Remdesivir

- Remdesivir can induce CYP enzymes, including CYP1A2, CYP2B6, and CYP3A4, but currently no data are available regarding its drug–drug interactions

Sofosbuvir

- In kidney transplant patients with HCV who were treated with sofosbuvir-ledipasvir, 21-31% decrease in TAC blood concentrations was detected during HCV treatment despite TAC dose escalations.
- This interaction may be due to improved hepatic function after HCV treatment rather than induction of metabolizing enzymes.
- In contrast, some supposed P-gP inhibition by sofosbuvir-ledipasvir that has the potential to increase CNIs/mTOR inhibitors exposure.

Ivermectin

- CsA may inhibit metabolism of ivermectin by inhibiting CYP3A4 and P-gp
- Increased concentration of ivermectin may result in increased ivermectin induced neurotoxicity

Favipiravir

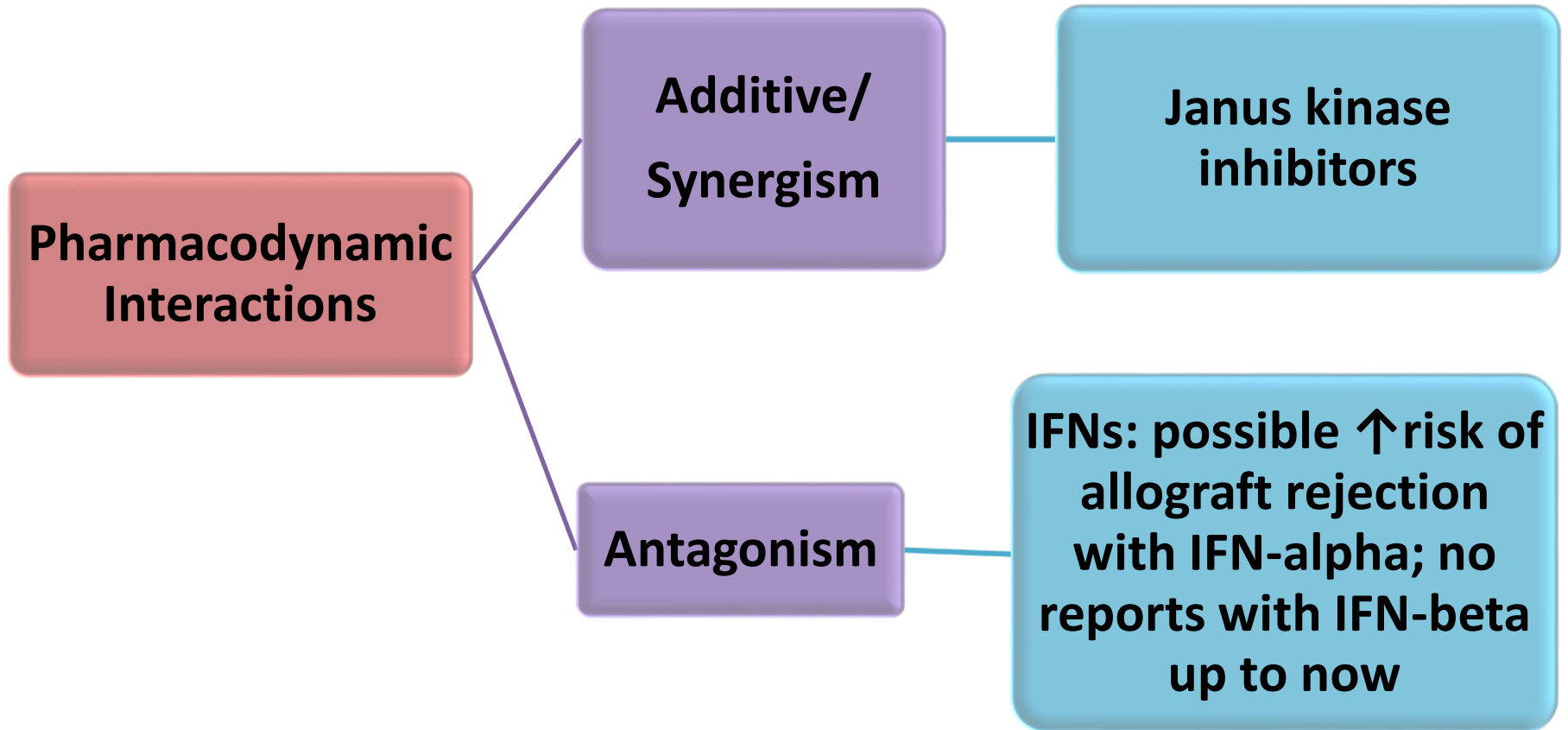
- No reported or suspected interaction

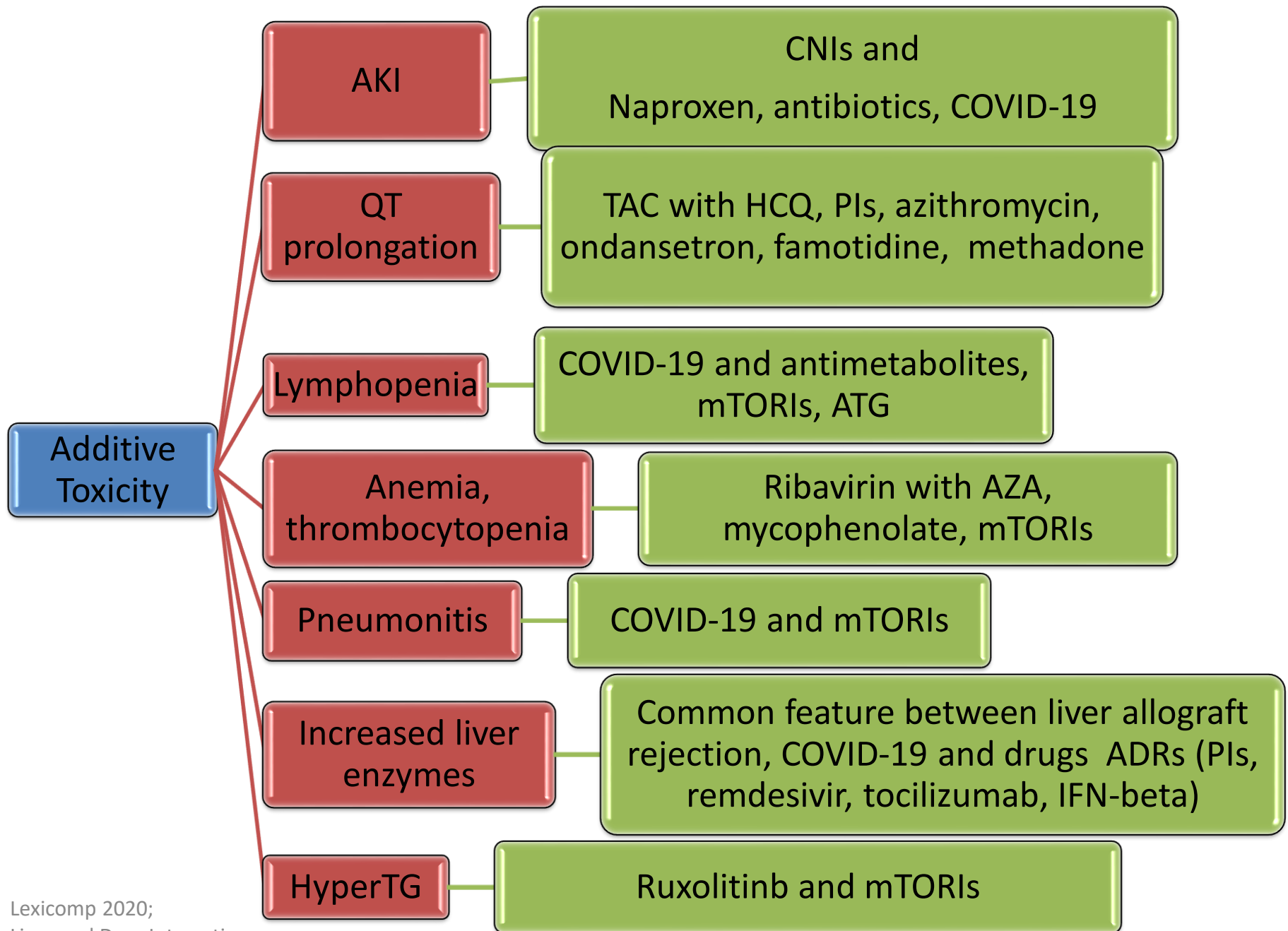
IL-6 and IL-1 Receptor Antagonists

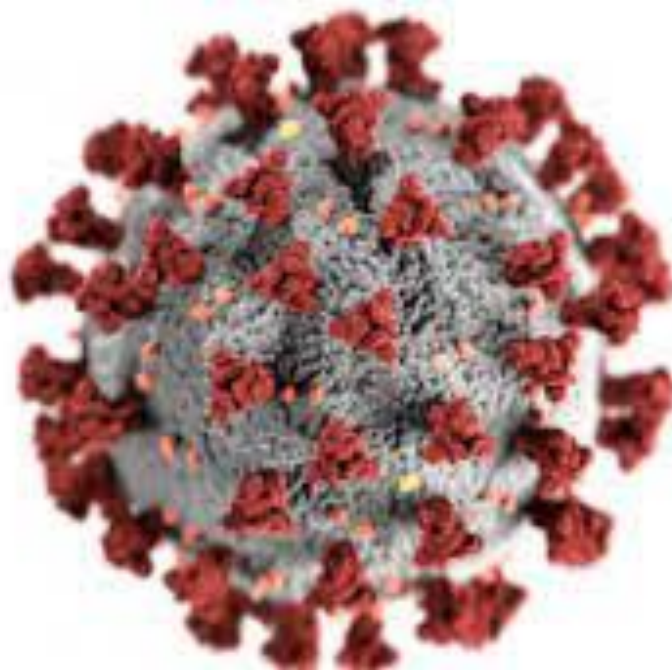
- IL-6 receptor antagonists (tocilizumab and sarilumab) and IL-1 receptor antagonist (anakinra) may decrease exposure to CNIs and mTORIs by inducing their metabolisms.
- IL-1 and IL-6 receptor antagonists do not have direct inducing effect on CYP isoenzymes or P-gP function; however, they may reverse suppressor effect of IL-1 and IL-6 on CYP isoenzymes.

Janus Associated Kinase Inhibitors (Ruxolitinib and Baricitinib)

- Although there is no report on co-administration of ruxolitinib with CNIs or mTORIs, ruxolitinib has the potential to inhibit P-gP in the intestine and increase the exposure to CNIs/mTORIs.
- Cyclosporine may also inhibit the metabolism of ruxolitinib through CYP3A4 isoenzyme.







Thank you For your Attention