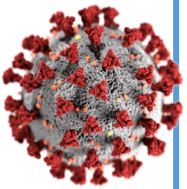


Early Key Events for CIAO COVID-19 AOP Design

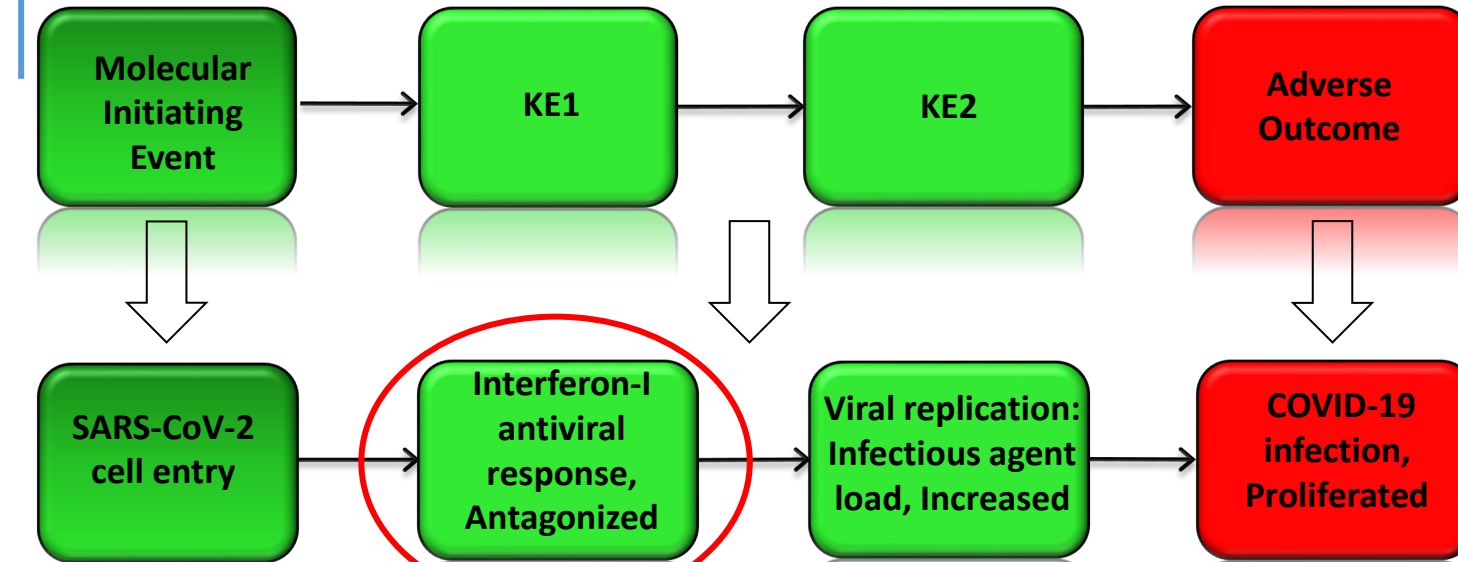
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Hub/Lung Working Group Meeting March 25, 2021



Early Molecular/Cellular Key Events (all cell types/tissues that have ACE2)



Immune suppression in the early stage of COVID-19 disease. Tian et al. Nov 2020, *Nature Communications*. Immunosuppression and tight junction impairment occur in the early stage of COVID-19 infection; an activated immune response emerges later in moderate and severe cases in a second stage of the disease, potentially leading to cytokine storm and organ damage. “We propose a two-stage mechanism of pathogenesis for this unusual viral infection.”

Spike protein binding to ACE2 is the first step in cell entry; TMPRSS2 activation; Cathepsin-L; Furin; Neuropilin-1 also facilitate cell entry.
Vaccine and therapeutic targets

Cell entry and uncoating *Leads to* translation of ORF1ab as the first step in immune evasion process; NSPs and accessory ORFs block host proteins in the IFN-I signaling cascade.
Therapeutic targets

IFN-I antagonism *Leads to* viral genome replication and sub-genomic transcription and translation of structural and ORF proteins; viral proteins *modulate the cell environment and hijack host cell resources* to produce more virus, increasing viral load to transmission risk levels.
Therapeutic targets, testing

Viral load increase *Leads to* infection spread at all levels: cell-to-cell, human-to-human and cross-species transmission.
PPE, behavior, disinfection, institutional controls

Viral proteins and RNA also *Lead to* Immune Activation in later stages including PAMP and DAMP triggering of inflammatory responses, e.g., inflammasome, ROS, cytokine production and adaptive immune response, **covered under the disease progression AOPs**