

Knowledge systematization of COVID-19 infectious processes based on Homeostasis Imbalance Process (HoIP) Ontology

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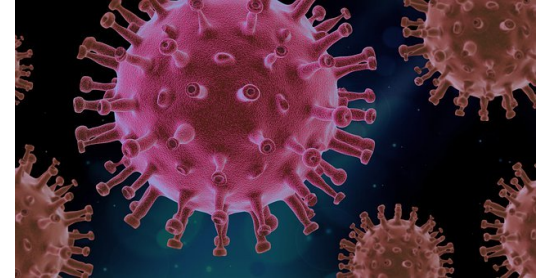
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WCO-2020 2020.10.27

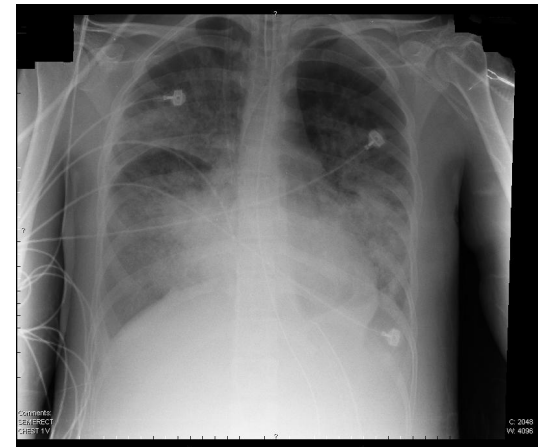
BACKGROUND

- One of the major issues in COVID-19 is the risk management of severity
E.g. Acute respiratory distress syndrome (ARDS)
- We need an understanding of the mechanisms of COVID-19



Objective

- Knowledge systematization of COVID-19 infectious processes based on ontology



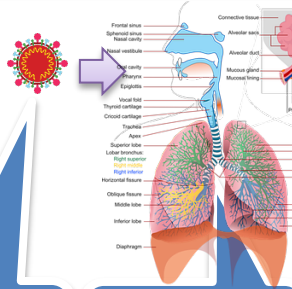
ARDS X-Ray

https://commons.wikimedia.org/wiki/File:ARDS_X-Ray.jpg#/media/ファイル:ARDS_X-Ray.jpg

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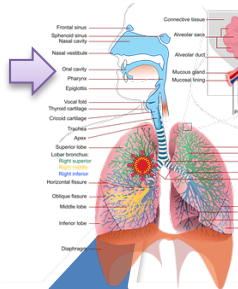
Invasion (Infection) stage

Manifestation stage



Attachment

Entry



Colonization

Proliferation



Clinical
manifestation

Infectious course: **A series of process** in an organism from viral attachment to clinical manifestations, which is not part of the life of the organism.

Concerning COVID-19,

A wide variety of processes among patients:

- No symptoms
- microthrombus formation
- processes related to acute respiratory distress syndrome (ARDS)

Focus on homeostasis imbalance processes
from non-symptoms to severe manifestation

Development of Homeostasis imbalance process (HoIP) ontology

Issue

- Clarifying processes from no symptoms to severe manifestation
- Coping with granularities in the body
- Distinction between COVID-19 and other diseases such as MERS
- Finding commonalities across multiple diseases



Our approach

- Introducing homeostasis imbalance model
- Functional decomposition approach
- Developing three-layer ontological structure

Homeostatic imbalance model

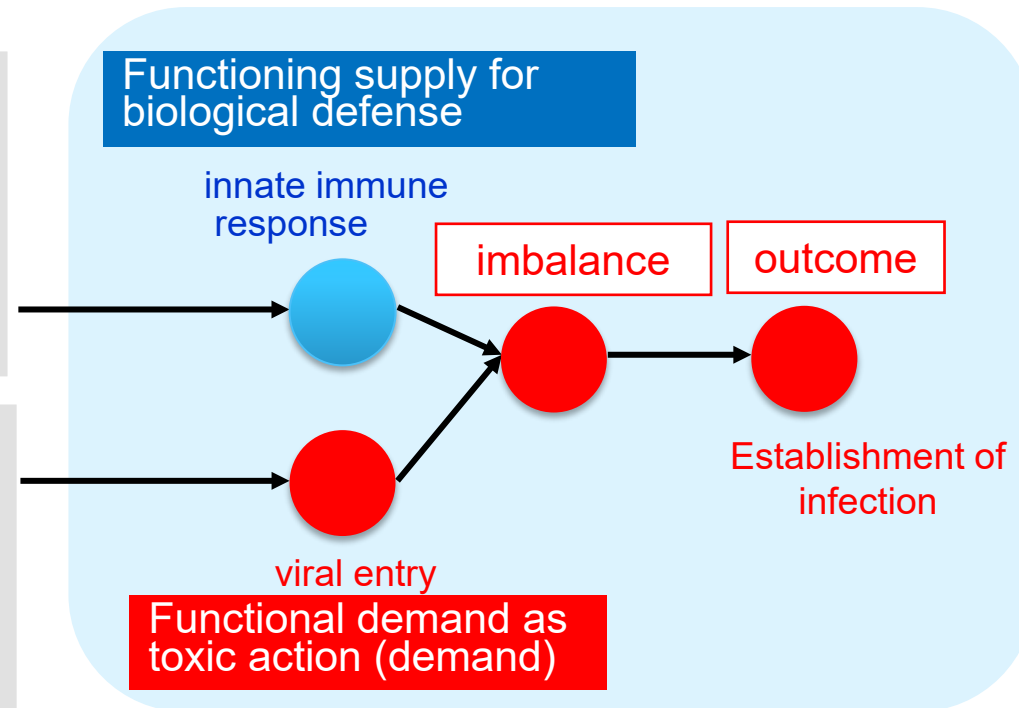
- Homeostatic imbalance model has four basic units:
 1. functional **supply** for **biological defense**,
 2. functional **demand** triggered by **viral action**,
 3. balance/**imbalance**,
 4. **outcome** from organelles, cells, to the organ of pathological manifestation

Functional supply

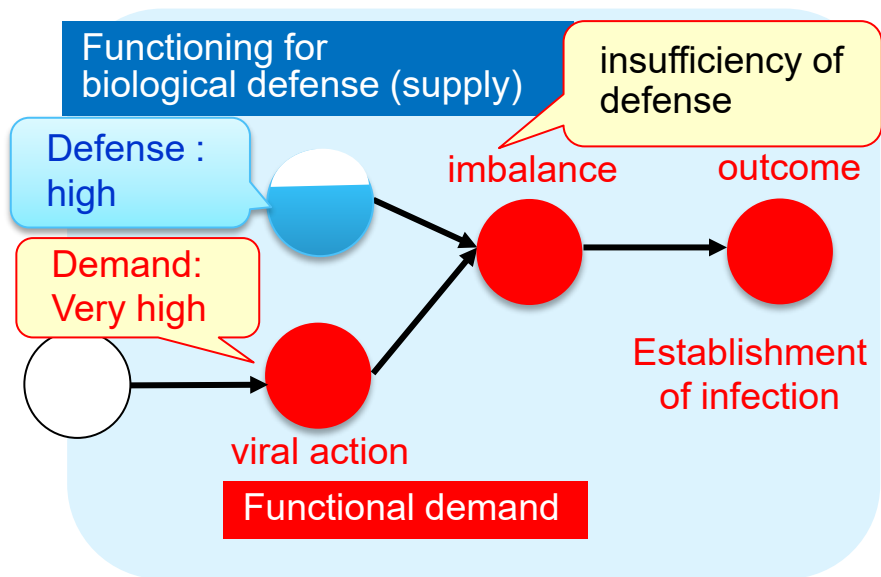
- Performing biological **defense function (supply)**
- E.g., innate immune response

Functional demand

- Process of required defense function (**functional demand**)
- E.g., viral entry

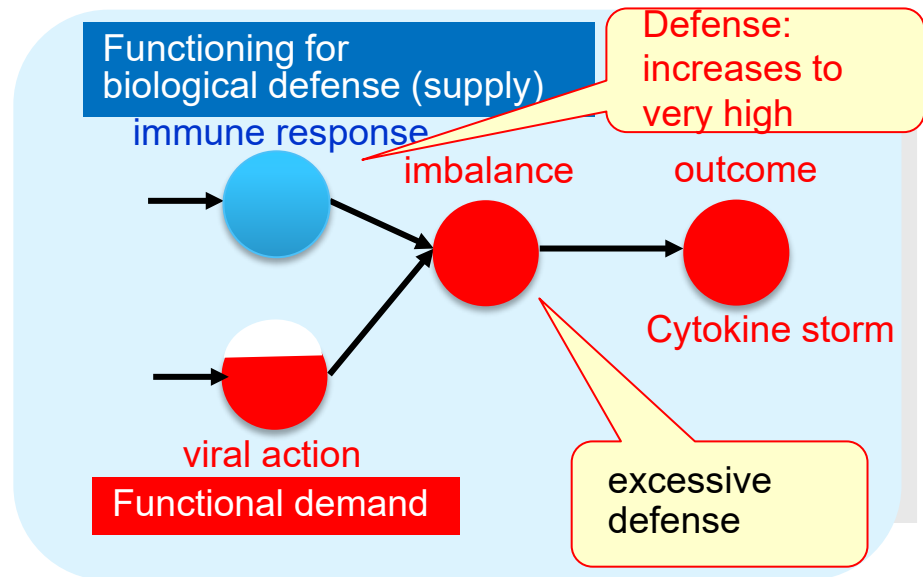


Severe outcome (excessive demand)



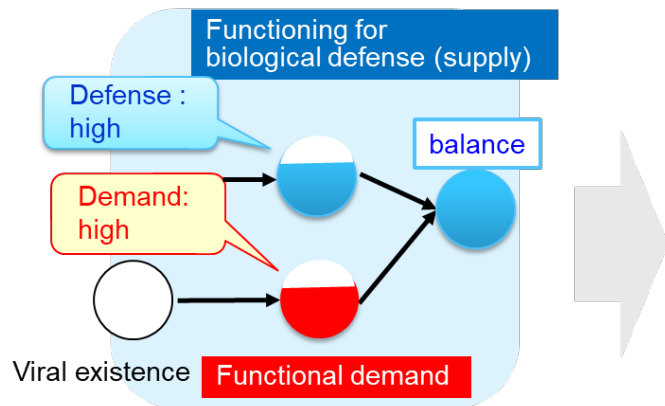
When **demand** becomes **very high**, the imbalance occurs, which brings about an outcome.

Severe outcome (excessive defense)



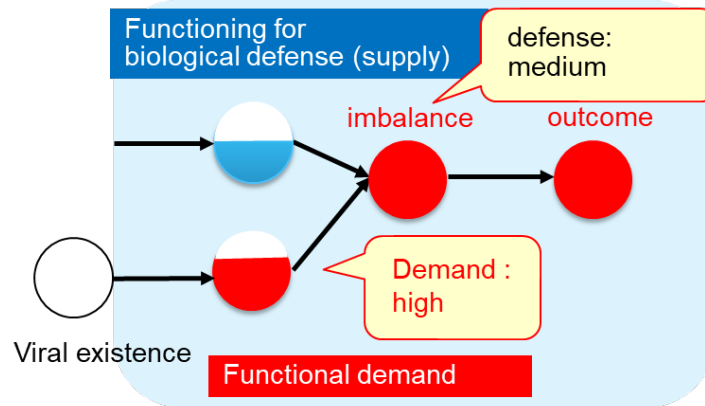
When **defense** becomes **very high** (**excessive defense**), the imbalance can also occur, which brings about an outcome.

Latent (to maintain high-level homeostasis)

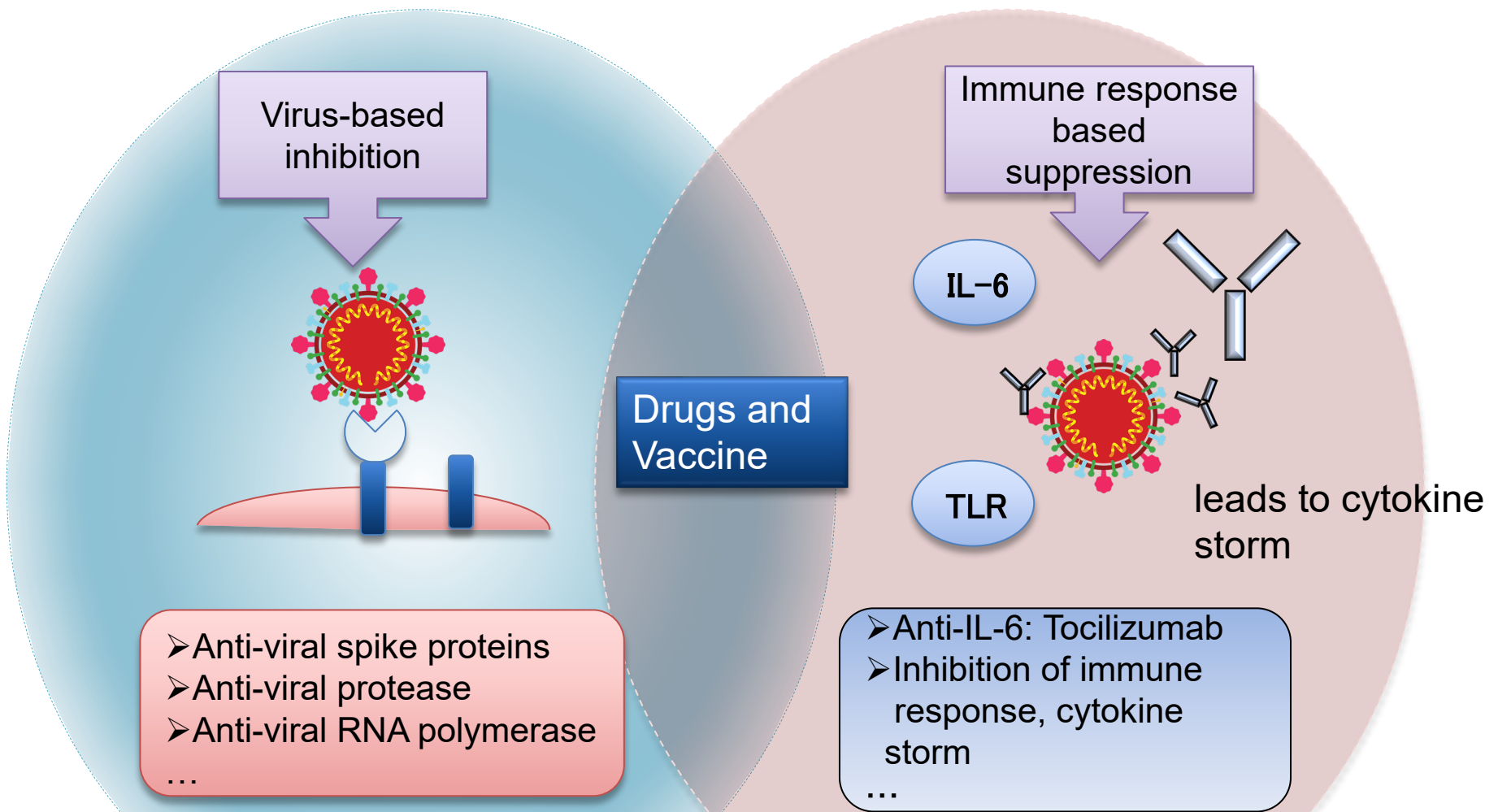


When demand increases to high, biological defense also increases and the balanced keeps at high level homeostasis than normal condition.

Manifestation (Adaptation failure)



When function decreases, an **imbalance** (insufficiency of biological defense function) occurs, which leads to manifestation as an **outcome**.



Imbalance model can

- distinguish viral action and innate immune response
- represent excessive defense, i.e., immune response, leading to the severe manifestation

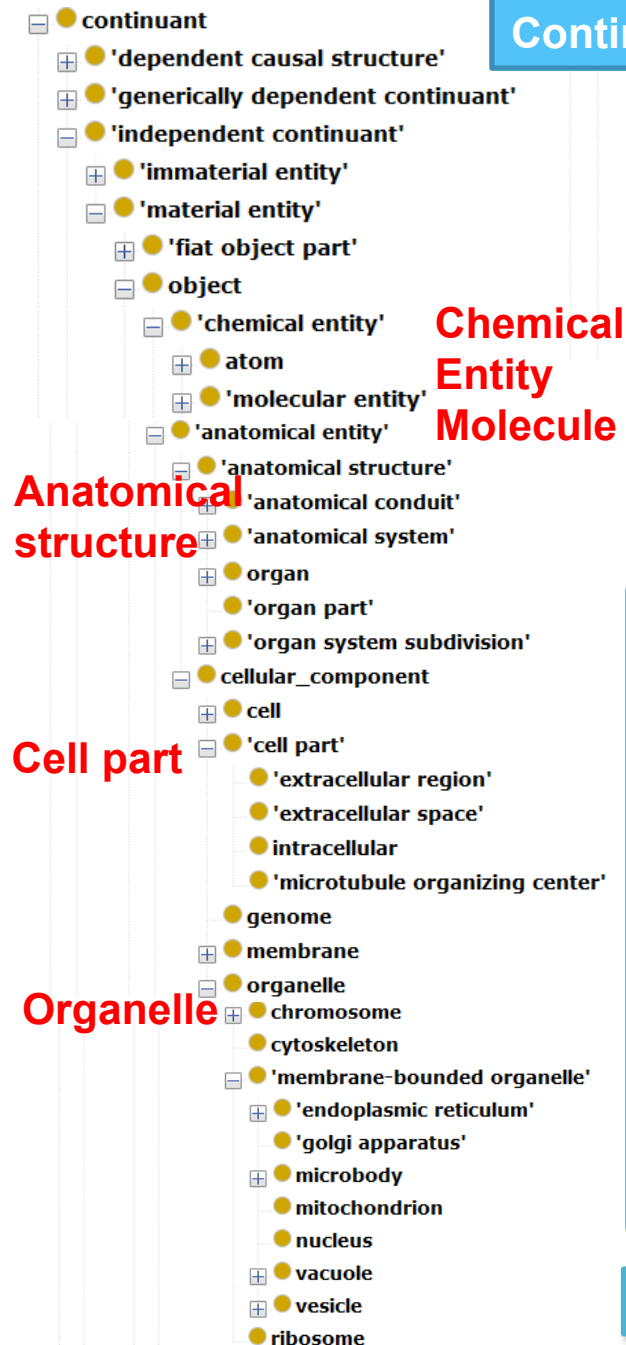
Our approach will support new drug development

Overview of HoLP

Tool: Protégé 5.5.0

Continuant

Occurrent

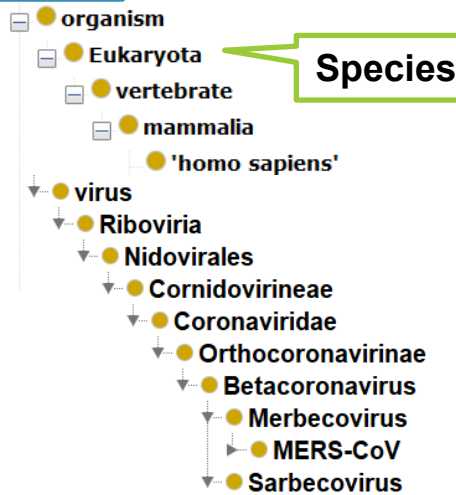


Chemical
Entity
Molecule

Anatomical
structure

Cell part

Organelle



Species

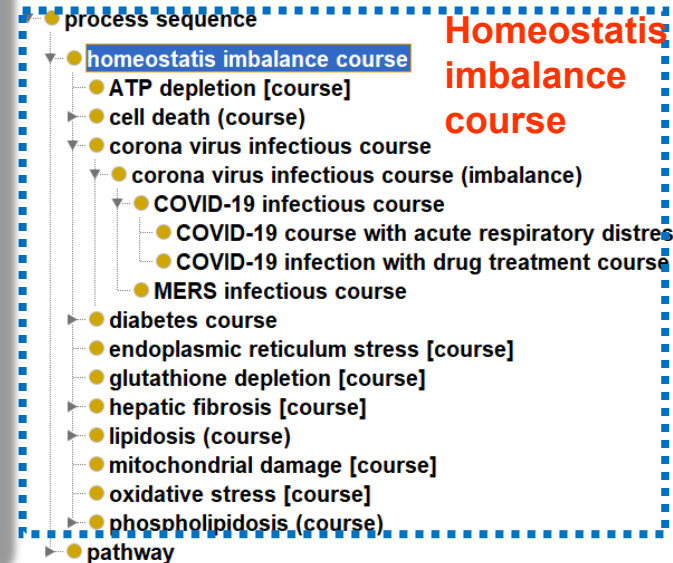
- Continuant (thing)
 - Molecule
 - Structure (organ, cell, organelle)
- Dependent continuant
 - Role
 - Quality
- Occurrent
 - Process
 - imbalance course

✳not shown
in the figure.

Process



Homeostatis
imbalance
course



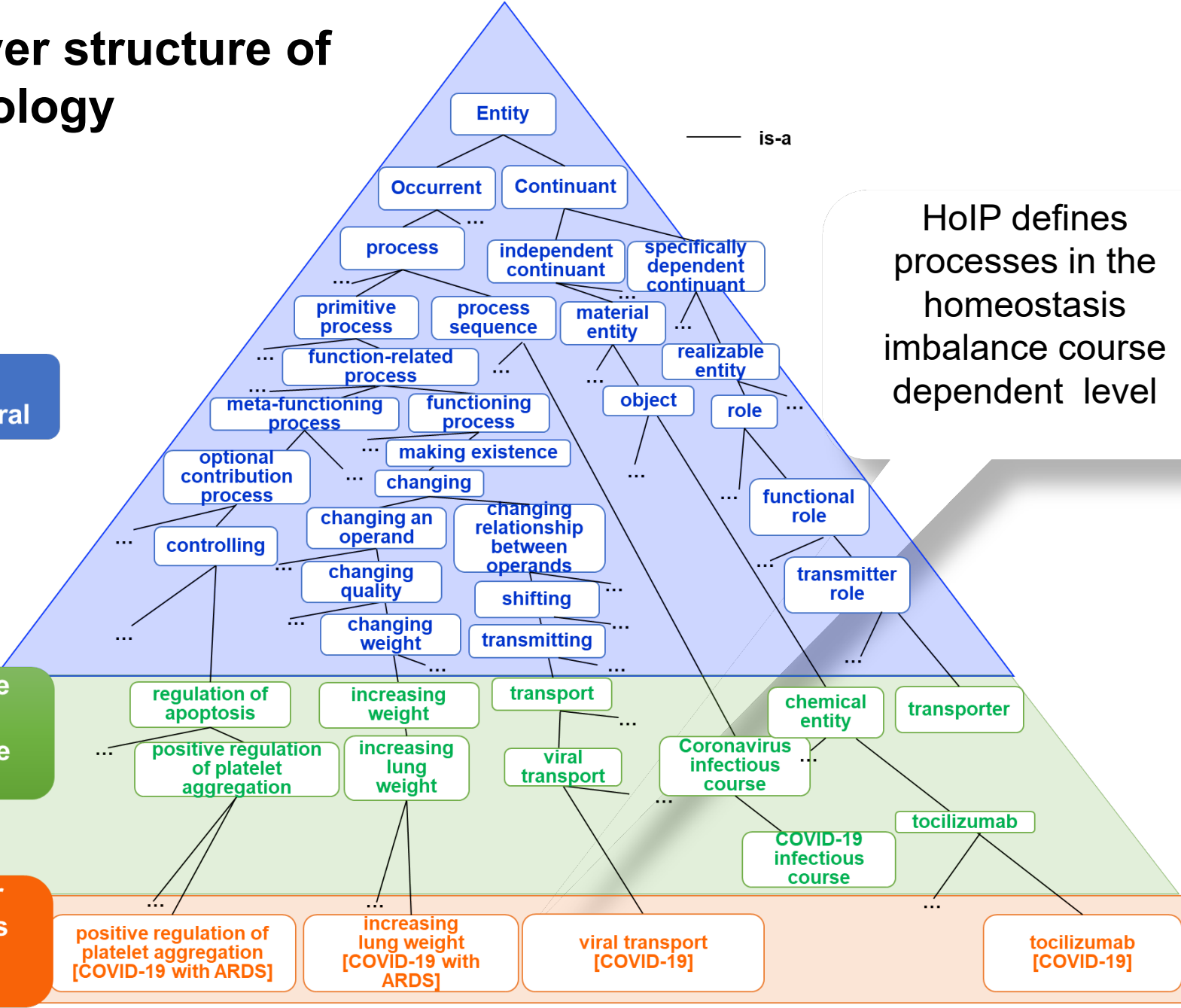
Total number : 9014 Axiom : 81382 (2020.10.14)

Three-layer structure of HoIP ontology

Top layer
Domain neutral

Intermediate layer
Biomedicine dependent

Lower layer
Coronavirus infection dependent



HoIP defines processes in the homeostasis imbalance course dependent level

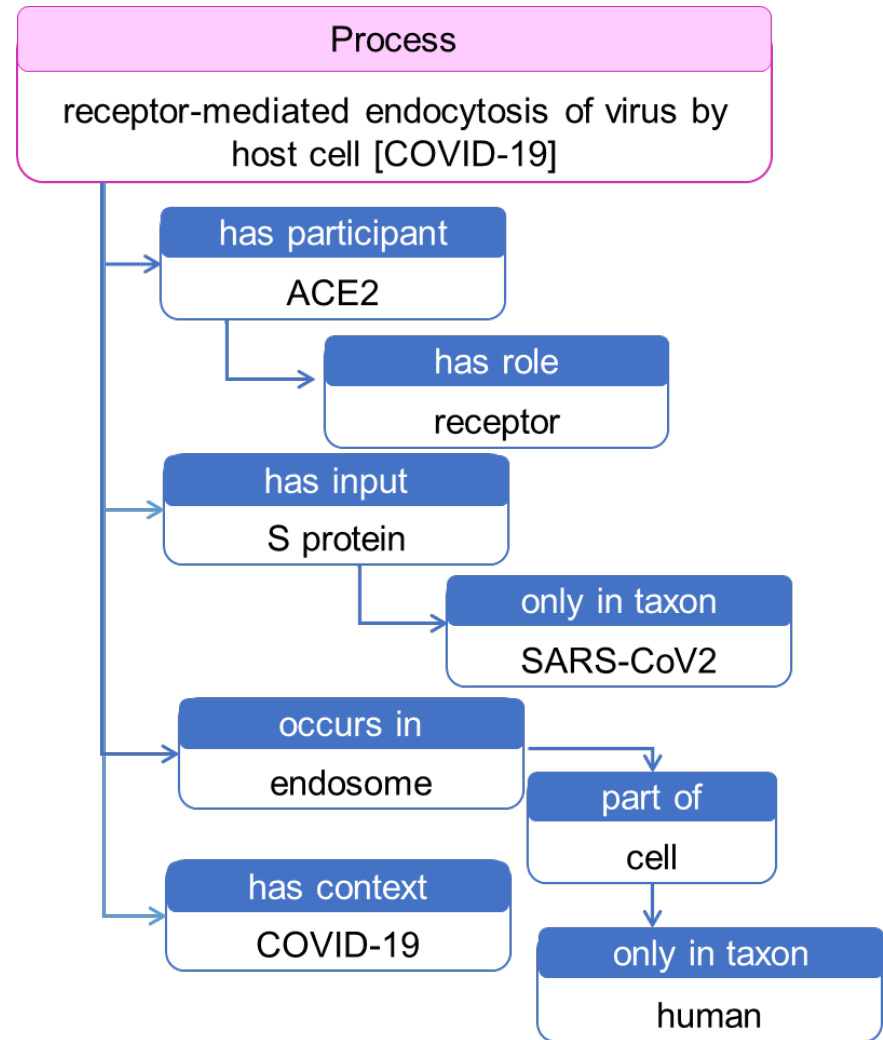
How to specifies the COVID-19 infectious process?

HoIP lower layer define processes:

- constitute a **specific course**
- **restrict properties** in the particular description.

e.g.), receptor-mediated endocytosis of virus by host cell [COVID-19]

- ‘has participant’ **ACE2**
 - ‘has role’ receptor
- ‘occurs in’ endosome
 - ‘part of’ cell and ‘only in taxon’ human
- ‘has context’ only **COVID-19 infectious course**



Top layer
Domain neutral

process

BFO

Intermediate layer
Biomedicine
dependent

receptor-mediated
endocytosis of virus
by host cell

GO

HoIP

Lower layer
coronavirus
infectious course
dependent

receptor-mediated
endocytosis of virus
by host cell [COVID-19]

receptor-mediated
endocytosis of virus
by host cell [MERS]

has participant

ACE2

has role
receptor

has input

S protein

only in taxon

SARS-CoV2

has context

COVID-19 infectious course

has participant

DPP4

has role
receptor

has input

S protein

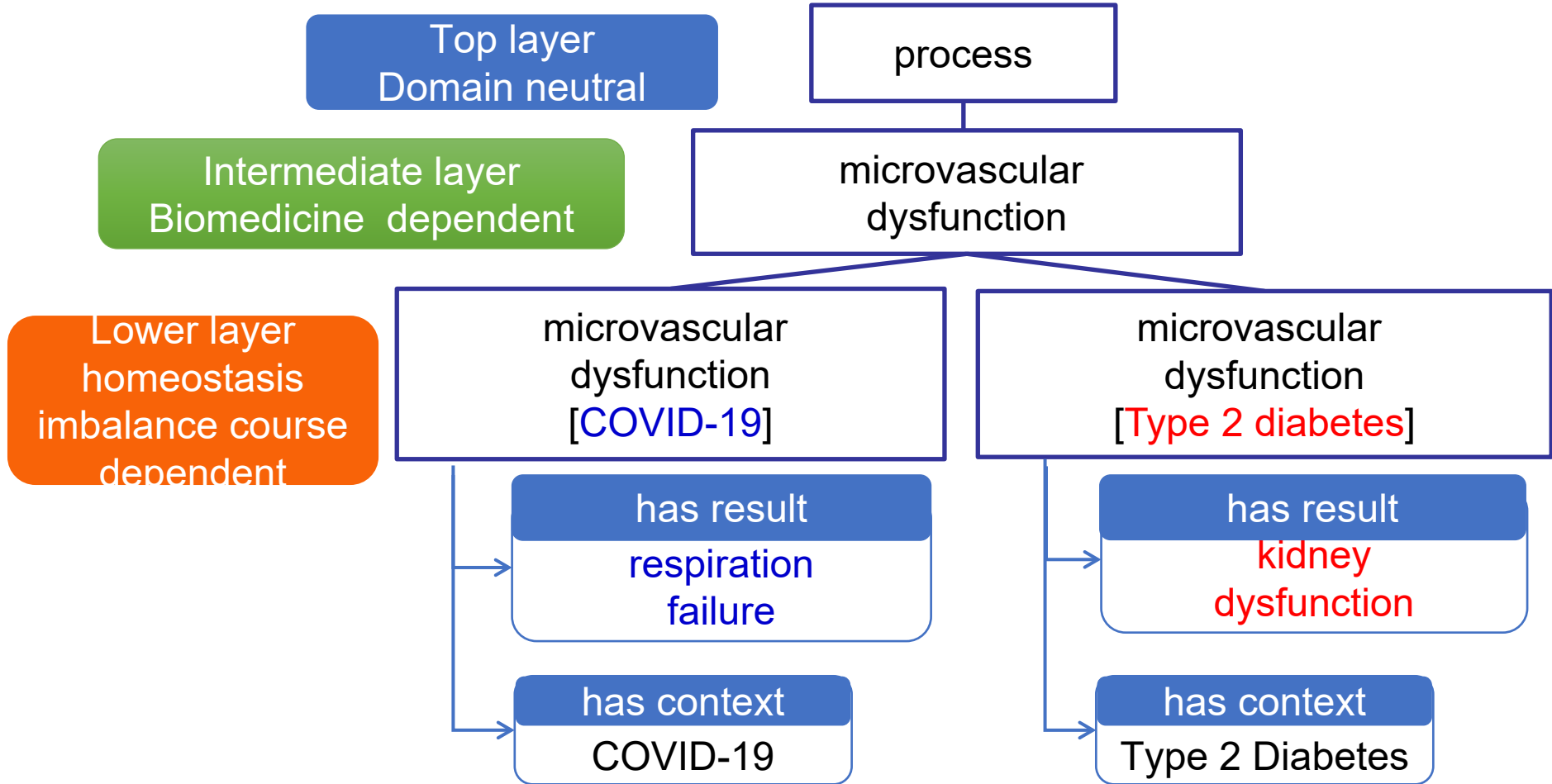
only in taxon

MERS-CoV

has context

MERS infectious course

Lower layer can
distinguish
COVID-19
processes from
MERS ones



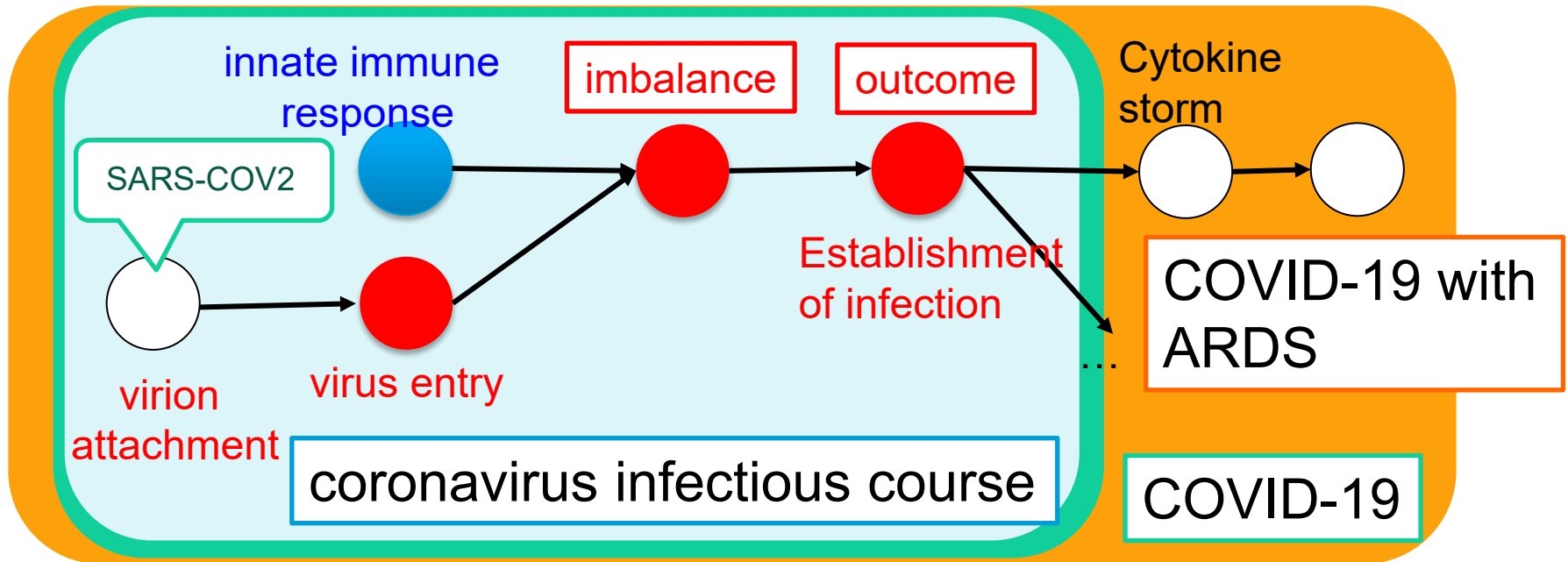
Our three-layer model can find

- common processes across multiple courses in the intermediate layer
e.g. microvascular dysfunction common to COVID-19 and Type2 diabetes

Coronavirus infectious course map

represents causal relationships of processes

→ causal relationship (has result)
○ process



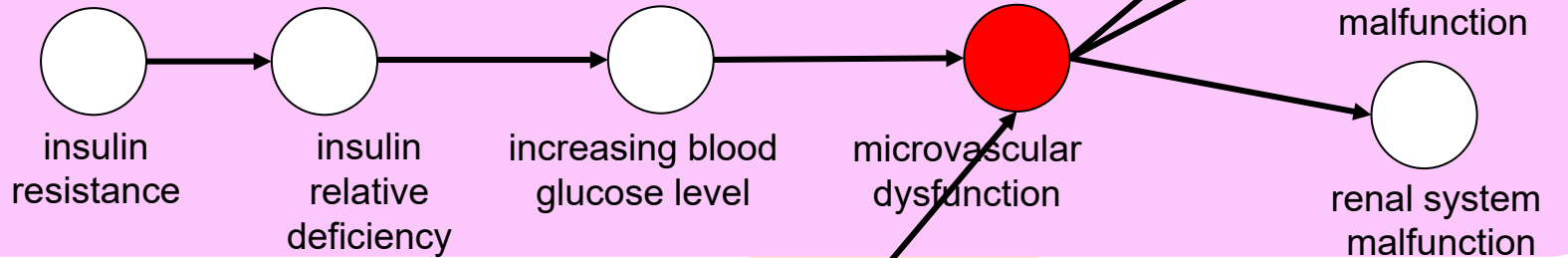
/s-a relation between courses is shown as an inclusion relationship

COVID-19 course includes the basic imbalance unit of the coronavirus course

/s-a relation

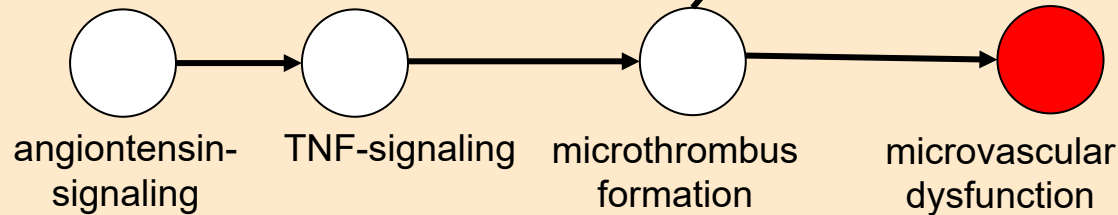
- corona virus infectious course (imbalance)
- COVID-19 infectious course
- COVID-19 course with acute respiratory distress syndrome

Type2 Diabetes

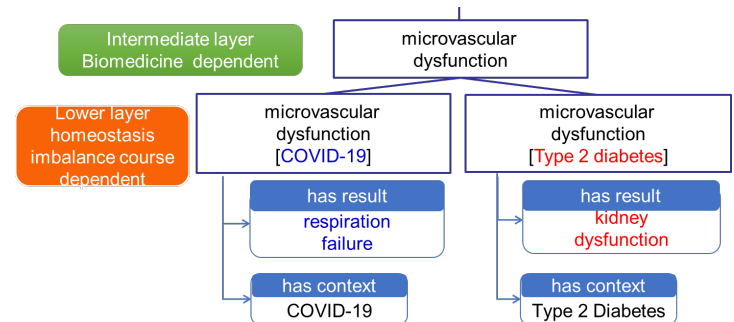


COVID-19 with ARDS

general causal relationships



Our approach can find potential severe risk patients and explain the unexpected severe manifestation in diabetes



Homeostasis infection process ontology (HoIP)

- HoIP is open to the public on BioPortal
- <https://bioportal.bioontology.org/ontologies/HOIP>

← → ↻ bioportal.bioontology.org/ontologies/HOIP

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Homeostasis imbalance process ontology

Last updated: September 1, 2020

[Download](#) [Link](#) [Home](#)

[Summary](#) [Classes](#) [Properties](#) [Notes](#) [Mappings](#) [Widgets](#)

Details

Acronym	HOIP
Visibility	Public
Description	Homeostasis imbalance process ontology (HoIP) is an ontology that systematizes a wide variety of terms involving homeostasis imbalance courses and processes. The alpha version of HoIP focuses on homeostasis imbalance triggered by virus actions concerning COVID-19 infectious processes.
Status	Alpha
Format	OWL
Contact	Yuki Yamagata, yuki.yamagata@riken.jp
Categories	Biological Process, Dysfunction

Metrics ?

Classes	9,013
Individuals	0
Properties	85
Maximum depth	15
Maximum number of children	726
Average number of children	3
Classes with a single child	1,629
Classes with more than 25 children	32
Classes with no definition	2,585

Submissions

Version	Released	Uploaded	Downloads
2020/09/01 (Parsed, Indexed, Metrics, Annotator)	09/01/2020	09/01/2020	OWL CSV RDF/XML Diff

Visits

1
0.8
0.6

GitHub <https://github.com/yuki-yamagata/hoip>

provides COVID-19 related information in HoIP

- COVID-19 infectious course map
- Entity list concerning COVID-19 infectious course

github.com/yuki-yamagata/hoip

yuki-yamagata / hoip

<> Code Issues Pull requests Actions Projects Wiki

master 1 branch 0 tags

yuki-yamagata latest version 0901

- COVID-19map Merge branch 'master' of https://github.com/yuki-yamagata/hoip
- Entity_list Entity_list up
- README.md Update README.md 10 days ago
- hoip.owl latest version 0901 8 days ago

Homeostasis imbalance process ontology

Homeostasis imbalance process ontology concerning COVID-19 infectious course and by virus actions concerning COVID-19 infectious course. The top layer contains general homeostasis imbalance process ontology, and the bottom layer contains biomedical terms, and the middle layer contains COVID-19 related terms.

macrophage interleukin-8 production [COVID-19 with ARDS]

Process_label	Participant	Participant_label
Inflammasome activation [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006043	NLRP3 (human)[coronavirus infectious disease]
Inflammasome activation [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006130	PYCARD (human)[coronavirus infectious disease]
Inflammasome activation [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006131	CASP1 (human)[coronavirus infectious disease]
IL-1beta processing [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006131	CASP1 (human)[coronavirus infectious disease]
IL-1beta processing [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0030051	IL-1B (human)[COVID-19 with ARDS]
IL-1beta production [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006131	CASP1 (human)[coronavirus infectious disease]
IL-1beta production [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0030051	IL-1B (human)[COVID-19 with ARDS]
Inflammatory cytokine gene expression (severe)[COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0007085	IL-6(human)[coronavirus infectious disease]
IL-6 signaling(severe) [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0007085	IL-6(human)[coronavirus infectious disease]
TLR9 signaling [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006156	TLR9(human)[COVID-19]
release of DNA from mitochondria [COVID-19 with ARDS]	http://www.ebi.ac.uk/efo/EFO_0008480	mitochondrial DNA
tumor necrosis factor production (severe) [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006151	TNF A (human)[COVID-19]
increasing blood AST concentration [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006225	GOT1 (human)[coronavirus infectious disease]
increasing blood ALT concentration [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006228	GPT (human) [coronavirus infectious disease]
macrophage interleukin-8 production [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006009	CXCL8 (human) [COVID-19]
macrophage interleukin-8 production [COVID-19 with ARDS]	http://purl.obolibrary.org/obo/CL_0000235	macrophage
neutrophil chemotaxis[COVID-19 with ARDS]	http://purl.obolibrary.org/obo/CL_0000775	neutrophil
IL-17 signaling [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006385	IL-17A(human)[coronavirus infectious disease]
T-helper 17 cell cytokine production [COVID-19 with ARDS]	http://bioportal.bioontology.org/ontology/HOIP/HOIP_0006385	IL-17A(human)[coronavirus infectious disease]

Future Work

- Refinement and addition of processes of the COVID-19 in HoIP Ontology
 - Investigation of relationships of other diseases (diabetes, heart disease, etc.)
 - Investigation of differences in aging populations (elderly, child)
- Development of application system for visualization map
- Coordination of HoIP ontology with other ontologies such as CIDO and COVID-19-IDO for better understanding of COVID-19

Thank you