

Wittwehr et al.:

Understanding COVID-19 through Adverse Outcome Pathways – CIAO 2nd AOP Design Workshop

Supplementary Data

Annex A: Participant list

The following members of the CIAO crowd were connected – at least part of the time – to the Zoom conference call:

Amigó Grau, Núria	Biosfer Teslab	Spain
Amorim, Maria João	Instituto Gulbenkian de Ciência – Fundação Calouste Gulbenkian	Portugal
Batista Leite, Sofia	European Commission, Joint Research Centre (JRC)	EU
Beronius, Anna	Karolinska Institutet	Sweden
Bezemer, Gillina	Impact Station	The Netherlands
Bostroem, Ann-Charlotte	European Commission, Joint Research Centre (JRC)	EU
Clerbaux, Laure-Alix	European Commission, Joint Research Centre (JRC)	EU
Coecke, Sandra	European Commission, Joint Research Centre (JRC)	EU
Daskalopoulos, Vangelis	European Commission, Joint Research Centre (JRC)	EU
Debernardi, Francesca	Ospedale Varese	Italy
Filipovska, Julija	Independent	North Macedonia
Garcia-Reyero, Natàlia	U.S. Army Engineer Research and Development Center (ERDC)	USA
Gavins, Felicity	Brunel University London	United Kingdom
Halappanavar, Sabina	Health Canada	Canada
Hargreaves, Alan	Nottingham Trent University	United Kingdom
Hogberg, Helena	Johns Hopkins University	USA
Huynh, Mylene	TruPoint Health	USA
Jacobson, Daniel	Oak Ridge National Laboratory	USA
Kim, Youngjun	KIST Europe Forschungsgesellschaft mbH	Germany
Kong, Hyunjoon	University of Illinois at Urbana-Champaign	USA
Krebs, Catharine	Physicians Committee for Responsible Medicine (PCRM)	USA
Lam, Ann	Green Neuroscience Laboratory, NeuroInx Research Institute	USA
Landesmann, Brigitte	European Commission, Joint Research Centre (JRC)	EU
Layton, Adrienne	U.S. Consumer Product Safety Commission	USA
Lee, Yong Oh	Korea Institute of Science and Technology Europe GmbH	Germany
Macmillan, Donna	Humane Society International (HSI)	United Kingdom
Magalhaes, Sandra	University of New Brunswick	Canada
Mantovani, Alberto	Istituto Superiore di Sanità – National Health Institute of Italy	Italy
Margiotto-Casaluci, Luigi	Brunel University London	United Kingdom
Martens, Marvin	Maastricht University	The Netherlands
Masereeuw, Roos	Utrecht University	The Netherlands
Mayasich, Sally	ORISE at U.S. Environmental Protection Agency	USA
Mei, Liang	US EPA/ORD	USA
Munoz-Pineiro, Amalia	European Commission, Joint Research Centre (JRC)	EU
Nymark, Penny	Institute of Environmental Medicine, Karolinska Institute	Sweden
Ohayon, Elan	Green Neuroscience Laboratory, NeuroInx Research Institute	USA
Ojasi, Joshi	N/A	India
Paini, Alicia	European Commission, Joint Research Centre (JRC)	EU
Parissis, Nikolaos	European Commission, Joint Research Centre (JRC)	Italy
Pistollato, Francesca	European Commission, Joint Research Centre (JRC)	EU
Price, Anna	European Commission, Joint Research Centre (JRC)	EU
Sachana, Magda	Organisation for Economic Co-operation and Development (OECD)	France
Sewald, Katherina	Fraunhofer ITEM	Germany
Sørli, Jorid	The National Research Centre for the Working Environment	Denmark
Sullivan, Kristie	Physicians Committee for Responsible Medicine (PCRM)	USA
Sund, Jukka	European Commission, Joint Research Centre (JRC)	EU
Surat, Parvatam	Centre for Predictive Human Model Systems, Centre for Cellular and Molecular Biology	India
Tanabe, Shihori	National Institute of Health Sciences	Japan
Tsaioun, Katya	EBTC at Johns Hopkins Bloomberg School of Public Health	USA

Vinken, Mathieu	Vrije Universiteit Brussel	Belgium
Viviani, Laura	Humane Society International (HSI)	Italy
Waspe, Jenny	Sheffield Hospital	United Kingdom
Willett, Kate	Humane Society International (HSI)	USA
Wittwehr, Clemens	European Commission, Joint Research Centre (JRC)	EU
Yepiskoposyan, Hasmik	Philip Morris International	Switzerland

Annex B: Key events

CIAO ID	Key event (KE)	Level of biological organisation	KE position	WG	Existing KE (AOP-Wiki)	Relevant existing AOPs
1	ACE2 receptor binding	1. molecular	1. MIE	green	1739 (ACE2 binding to viral S-protein)	
24	ACE2 receptor binding, sustentacular and basal cells	1. molecular	1. MIE	red		
34	ACE2 receptor binding, mitral/tufted cells/astrocytes/pericytes	1. molecular	1. MIE	red		
35	ACE2 receptor binding, olfactory epithelium	1. molecular	1. MIE	red		
36	ACE2 receptor binding, CNS (endothelial, neuronal and glial cells)	1. molecular	1. MIE	red		
41	ACE2 receptor binding, endothelial cells	1. molecular	1. MIE	green		
51	ACE2 receptor binding, pericytes	1. molecular	1. MIE	red		
64	ACE2 receptor binding, liver cells	1. molecular	1. MIE	red		
68	ACE2 receptor binding, kidney cells	1. molecular	1. MIE	red		
2	TMPRSS2 activation	1. molecular	2. early	green, red		
3	Neuropilin-1 binding	1. molecular	2. early	green		
4	Translation host/viral	1. molecular	2. early	green		
5	Viral transcription	1. molecular	2. early	green		
6	Viral replication	1. molecular	2. early	green	1738 (Enhanced viral entry and gene expression)	
7	Innate immune evasion	1. molecular/cellular	2. early	green		
8	ACE2 expression, decrease	1. molecular	2. early	green		
9	RAS imbalance	1. molecular	2. early	green		
10	ACE2 dysregulation	1. molecular	2. early	orange, yellow, green		
59	Angiotensin 1-7, decreased	1. molecular	2. early	red		
60	Angiotensin II, decreased	1. molecular	2. early	red		
65	Cell death (pyroptosis/necroptosis/apoptosis)	2. cellular	2. early	yellow	1825 (Cell death)	
73	Toll like receptors, dysregulation	1. molecular	2. early	green, orange		
11	Lung surfactant function, decrease	3. tissue	3. middle	yellow	1672 (Inhibition of lung surfactant function)	
12	Alveolar membrane integrity loss (lungs)	2. cellular	3. middle	yellow	1498 (Loss of alveolar capillary membrane integrity)	AOP 173 ²
13	Coagulation, increase	1. molecular	3. middle	orange, yellow		
14	Bradykinin system, activated	1. molecular	3. middle	orange		
15	Fibrinolysis, decrease	1. molecular	3. middle	orange		
16	Oxidative stress	2. cellular	3. middle	orange	1392 (Oxidative stress) or others	
17	NLRP3 inflammasome, activation	1. molecular	3. middle	orange		
18	Tissue resident cell activation	2. cellular	3. middle	orange	1492 (Tissue resident cell activation)	
19	Increased pro-inflammatory mediators	2. cellular	3. middle	orange	1493 (Increased pro-inflammatory mediators) or 1496 (Increased, secretion)	AOP 173 ²

² See <https://aopwiki.org/aops/173>

					of proinflammatory and profibrotic mediators)	
20	Leukocyte recruitment/activation	2. cellular	3. middle	orange	1494 (Leukocyte recruitment/activation) or 1497 (Increased, recruitment of inflammatory cells)	AOP 173 ²
21	Neutrophil-platelet interaction	2. cellular	3. middle	orange		
22	Hyperinflammation/systemic inflammation	3. tissue	3. middle	orange, red		
25	Sustentacular cells death	2. cellular	3. middle	red		
26	Damage/death olfactory sensory neurons	2. cellular	3. middle	red		
29	Sustentacular cells regeneration	2. cellular	3. middle	red		
30	Disruption blood brain barrier	3. tissue	3. middle	red		
31	Regeneration olfactory neurons	2. cellular	3. middle	red		
33	Neuroepithelial regeneration	2. cellular	3. middle	red		
42	Tissue factor activation	1. molecular	3. middle	yellow, orange, red		
43	Endothelial cell disruption, prothrombotic expression	1. molecular/cellular	3. middle	yellow, orange, red		
44	HMWK, increase	1. molecular	3. middle	yellow, orange, red		
45	Platelet aggregation	1. molecular	3. middle	yellow, orange, red	1375 (Increase, platelet aggregation)	
46	Fibrin clot formation	1. molecular	3. middle	yellow, orange, red		
66	Inflammation, liver	3. tissue	3. middle	orange, red	902 (Inflammation, liver)	
69	Cell death, kidney cells	2. cellular	3. middle	yellow, red	709 (Increase, cytotoxicity (renal tubular cell))	
23	Neuroinflammation	3. tissue	4. late	orange, red	188 (Neuroinflammation)	
27	Olfactory epithelium degeneration	2. cellular	4. late	red		
32	Neuroepithelial atrophy	2. cellular	4. late	red		
37	Neurodegeneration	3. tissue	4. late	red	352 (N/A, Neurodegeneration)	
48	Hypoxia	2. cellular	4. late	red	1678 (Impaired oxygenation of the blood)	
54	Hypertrophy (heart)	3. tissue	4. late	red	1043 (Hypertrophy/hyperplasia, smooth muscle) (?)	
55	Ischemia	3. tissue	4. late	red		
56	Microvascular dysfunction	3. tissue	4. late	red		
57	Coronary artery vasoconstriction	3. tissue	4. late	red		
61	Blood pressure, increase	3. tissue/organ	4. late	red	952 (Hypertension)	
62	Myocardial injury	4. organ	4. late	red		
28	Anosmia	3. tissue/organ	5. AO	red		
38	Seizures/epilepsy	5. individual	5. AO	red		
39	Encephalitis	4. organ	5. AO	red		
40	MS (multiple sclerosis)	4. organ	5. AO	red		
47	Sepsis	5. individual	5. AO	red		
49	Disseminated intravascular coagulation	3. tissue	5. AO	red		
50	Multi-organ failure	4. organ	5. AO	red		
52	Stroke/cerebrovascular disease	4. organ/individual	5. AO	red		
53	Lung fibrosis	4. organ	5. AO	red	1458 (Pulmonary fibrosis)	AOP 173 ²
58	Thrombosis	3. tissue	5. AO	orange, red		
63	Heart failure	4. organ	5. AO	red	1535 (Heart failure)	
67	Liver injury	4. organ	5. AO	red	1549 (Liver injury)	
70	Kidney injury	4. organ	5. AO	red	814 (Occurrence, kidney toxicity)	

71	Acute respiratory distress syndrome (ARDS)	4. organ	5. AO	yellow, orange (red?)	1748 (Increase, the risk of acute respiratory failure)	
72	Mortality	5. individual	5. AO	?		
74	Multi-scale KEs	6. multi-scale	6. several	orange		