The CIAO project "Modelling the COVID-19 Pathogenesis using the Adverse Outcome Pathways" – Report of the 4th online Workshop.

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Abstract

The CIAO project "Modelling the Pathogenesis of COVID-19 using the Adverse Outcome Pathway (AOP) framework" aims at organizing the available knowledge on the biological mechanisms underlying COVID-19 pathogenesis using the AOP framework. On 15th-16th September 2021, around 40 scientists from different fields of expertise met for the 4th online CIAO Workshop. During the workshop, the 15 AOPs depicting adverse outcomes observed in COVID-19 patients and developed so far within the project were recapitulated and assembled in a preliminary network, highlighting the interrelation between the various outcomes, the knowledge gaps and the importance of harmonized ontology. As CIAO relies on an interdisciplinary AOP-aligned crowdsourcing effort, the lessons learned from the collaborative process itself to inform on potential evolution of the framework were discussed. Factors modulating the disease outcomes were debated in terms of definition and integration into the AOP-Wiki. To conclude the workshop, it was decided that all the components of the AOPs will be further consolidated into the AOP-Wiki while the ongoing diverse publications will be continued.

1. Introduction

1.1 The CIAO project

The CIAO project aims to make sense of the overwhelming flow of data available on COVID-19 pathogenesis by exploiting the AOP framework (Nymark et al., 2021; Wittwehr et al., 2021). The AOPs depict the causal relationships that link the initial binding of the virus to ACE2 receptor over a series of biological key events (KE) toward an adverse outcome (AO), such as lung injury or multiorgan failure. The modular aspect of AOPs allows the development of AOP networks where shared KEs become evident and knowledge gaps can be identified (Villeneuve et al., 2019, 2014). Such mechanistic organization of the COVID-19 knowledge also helps to capture the various factors influencing the clinical outcomes. Developing AOPs modelling COVID-19 pathogenesis relies on interdisciplinary collaborative effort, synergizing exchange between experts from different fields. In addition, the application of the AOP framework to map a viral disease of high societal relevance provides novel outputs which can inform on potential needs for changes and adaptations of the framework itself (Carusi et al., 2018; Nymark et al., 2021).

Around 75 scientists from all over the world are currently participating in the project. The work within the project is organized among working groups (WG) focusing on the different outcomes of the disease and on different aspects of the project (Table 1).

Table 1. CIAO working groups (WG)

Working group name	Focus
Hub and Lung AOP group	KEs common to multiple COVID-19 AOs (e.g. coagulation, hyperinflammation) joint with pulmonary AOPs
Multi-organ integration AOP group	AOPs and KEs specific to liver, kidney, heart and gut
Neuro AOP group	AOPs and KEs linked to neuropathological conditions (anosmia, seizures, epilepsy, encephalitis, …)
Literature Review group	Applying systematic literature review to support AOP development (neuro pilot study)
Modulating Factors group	Integrate modulating factors into KEs/KERs/AOPs
Multiscale Impact group	Elucidate the multiscale factors of COVID-19 across levels and time and evolve the AOPs to address those multiscale aspects
AOP network team	Build up an AOP network based on the COVID-19 related KEs and AOPs already entered in the AOP-Wiki
Meta-level paper team	Evaluate how the AOP framework and the crowdsourcing effort were applied to a viral disease

In October 2020, January 2021 and April 2021, the first three online CIAO workshops were held (www.ciao-covid.net). On 15th-16th September 2021, the 4th CIAO workshop gathered around 40 participants over 2 half-days (Annex A). The workshop was facilitated by Laure-Alix Clerbaux and all the coordination team.

1.2 Goals of the 4th CIAO AOP Workshop

After a warm up session and welcoming slides to introduce the newcomers (Annex A), the goals to be achieved during this workshop were presented. The will was expressed to shape the workshop around discussions to examine cross-cutting challenges faced in each WG and find ways forward during the workshop. The first agenda item was therefore, centered on the building up of the COVID-19 AOP network assembling all the AOPs developed so far within the different WGs. Current network issues and ways to harmonize the ontology were discussed. The second agenda item related to exploring the success and challenges in applying the AOP framework via interdisciplinary collaboration to model a viral disease. The third agenda item was dedicated to present the CIAO Ground rules. The fourth goal of the workshop was to properly define what a Modulating Factor (MF) is, identify the challenges in integrating them into the AOP-Wiki platform and propose ways forward.

2. The CIAO AOP network

The modular structure of AOPs, composed of reusable components (KE) developed previously within other research fields (such as toxicology) or within CIAO, allows for development of an AOP network where the interrelation of the many COVID-19 outcomes and central mechanisms are brought to light.

2.1 AOPs modelling COVID-19 in the AOP-Wiki

A recap of the 15 AOPs depicting COVID-19 central, pulmonary, neurological and multi-organ AOs developed so far and already uploaded into the AOP-Wiki (Annex B) was presented. The AOPs are built on 59 KEs, of which 26 were already included in the AOP-Wiki and 33 were developed within CIAO. The levels of details and completeness of the CIAO AOPs varied. All participants could identify if a KE or an AOP was missing or misspelled.

2.2 The CIAO AOP network

The CIAO AOP network was developed through a series of iterative processes entailing i) gathering of basic information on all available AOPs, KEs, and KERs developed by members of the CIAO crowd, ii) processing of the gathered information in line with the FAIR (Findable, Accessible, Interoperable and Reusable) principles (Wilkinson et al., 2016) and iii) computational generation of a directed network.

The **first** step comprised review of AOPs available in the AOP-Wiki, CIAO group discussions during meetings and workshops, and personal discussions with specific members of the crowd. Overall, 18 individual AOPs currently in development were considered for inclusion in the network (including AOPs not yet in the AOP-Wiki).

The **second** step focused on processing and so called "FAIRification" of the gathered information and comprised aims to make the data *Findable* beyond the realm of the CIAO project, i.e. including persistent identifiers (IDs) such as AOP and KE IDs from the AOP-Wiki when available, as well as attempts to relate the descriptions of the AOPs/KEs to a COVID-19 ontology (Sargsyan et al., 2020). *Accessibility* to the data was ensured in most cases through the AOP-Wiki, however, as stated above some efforts to gather "offline" AOP/KE information was required for those not on AOP-Wiki already. Next, the information was made *Interoperable* both internally (among different AOPs) and with computational tools, by harmonization of AOP components in terms of descriptions (including considerations of ontology-inclusion) and processing of the information in order to provide computationally compatible data formats. Finally, the *Reusability* of the AOP network, and in particular the individual AOPs comprised in the network, will be ensured by publishing all AOPs included in the network under a CC BY 4.0 license, fully in line with the publication procedure in the AOP-Wiki.

The **third** step aimed at computational generation of a directed AOP network covering all information gathered in the previous steps. The publicly available program Cytoscape was used to support the network-generation, applying the app NetworkAnalyzer in order to analyze the network properties.

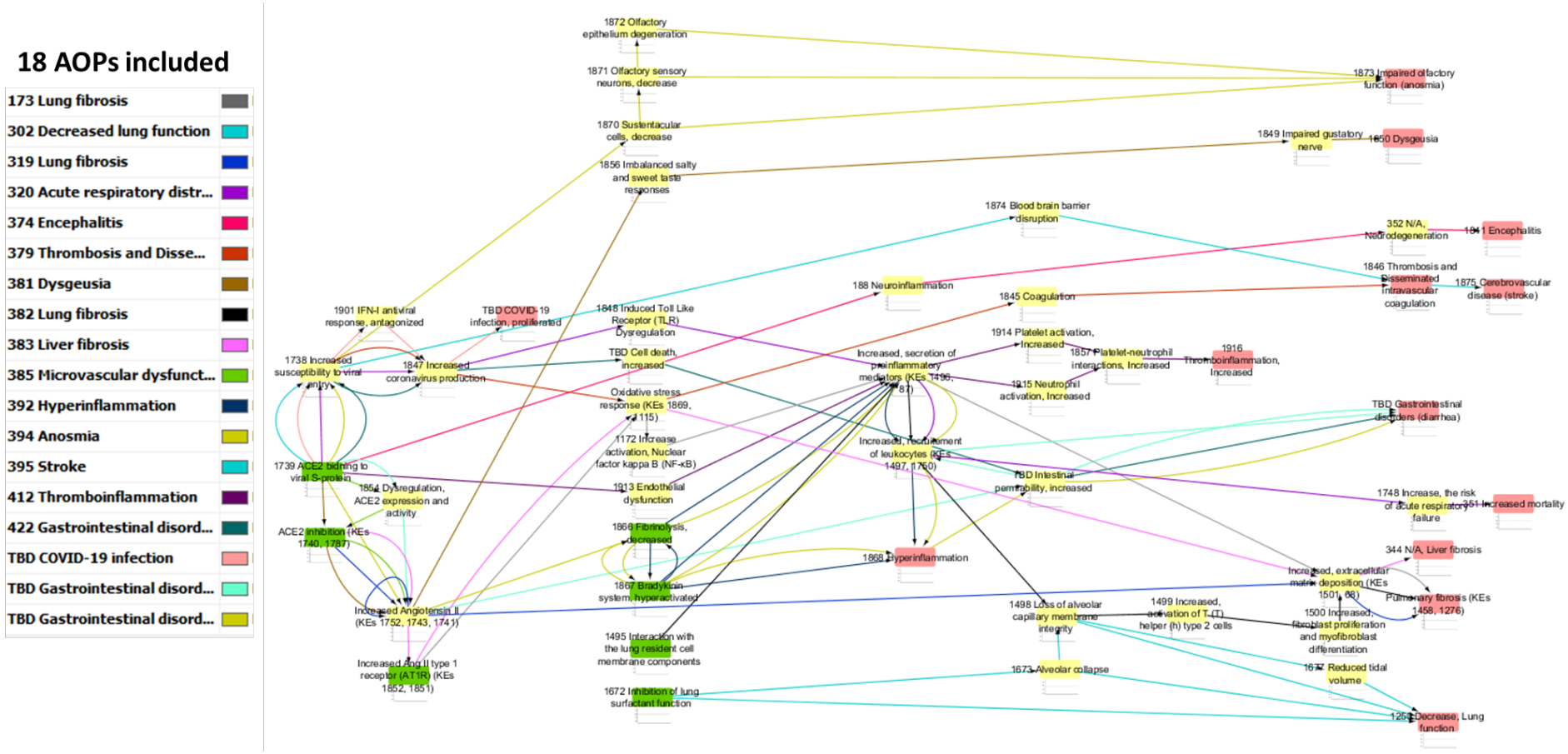

Figure 1. Current status of the AOP network modelling COVID-19 developed within CIAO.
Green nodes: MIEs; Yellow nodes: KEs; Red nodes: AOs. Each node is described with the corresponding KE ID and title, except in the case where similar KEs have been harmonized and a harmonized title is used followed by all related KE IDs within parentheses.

The results show a first draft CIAO AOP network including a selection of 18 CIAO AOPs considered mature enough to be included (of which 15 are accessible through the AOP-Wiki). Maturity was overall assessed through availability of KERs in each AOP. The network shows a clustering coefficient of 0.144 including 52 nodes, i.e. KEs. The average number of neighbors for each KE is 2.885 and the most highly connected KE is "Increased, secretion of proinflammatory mediators (KEs 1496, 87)" (15 connections; Figure 1).

The current network focuses on the lung as the target organ for the SARS-CoV2 entry, which leads to KEs/AOs associated with downstream injury, potentially culminating in organ dysfunction and failure. An AOP network modelling the neurological manifestations of COVID-19 was also presented and the question was raised if a parallel network with the brain as the entry route for the virus either potentially through the olfactory sensory neurons axons or through transynaptic transfer of SARS-CoV-2 from peripheral neurons should be considered.

The overall purpose of the network is to provide a visual and computationally analyzable overview of the work on AOP/KE/KER development within the CIAO project. Further work can be envisioned in order to refine the network from the perspective of i) further insight gained in the project and by the CIAO crowd regarding AOs related to COVID-19; ii) the need for further/adjusted connections in the network and/or separate networks for other routes of entry (such as neuronal) and/or increased viral replication, and iii) solutions involving inclusion of information regarding modulating factors.

2.3 BO group discussions

Following that presentation, the aim of the BO groups was presented. Participants were then divided in small breakout (BO) groups of +- 6 persons to discuss the same topic during 30 minutes: first "network inputs and issues" and then "ontology harmonization". The main points discussed and ways forward proposed were reported back by each group on one slide that were assembled and presented on Day 2.

2.3.1 BO 1: **"**Network inputs and issues"

Goals

BO aimed at discussing problems associated with the network at all levels. Given the importance of the data included in the AOP-Wiki, one of the objectives was to identify and discuss problems that CIAO members are having to introduce data into the AOP-Wiki at all levels (KEs, KERs, AOPs). In addition, as a first network was presented, CIAO members were also asked to identify issues with the network itself. Many examples were provided to facilitate the identification of pertinent topics for discussion.

Report back and discussion

Participants identified that despite the characteristic multiscale organization of an AOP, the current network has a higher weight upstream. The majority of the KEs cover the molecular level and less the organ levels, relevant for the local environmental integration. In some cases, this could be overcome by renaming the KEs. The lack of KEs and KERs integration was mentioned as well as the time aspect. These aspects should be covered in the next steps of the network development instead of integrating new KEs. Many participants mentioned their challenges and difficulties in elaborating the weight of evidence for the KER(s). Such

information is available in the OECD AOP Handbook guidance (OECD, 2018). However, it was decided that a **training on Weight-of-Evidence (WoE**) **in KERs** would be highly relevant for the CIAO crowd at this stage of the project.
In the discussion regarding the integration of different information, Clemens Wittwehr informed that visual depiction of AOPs, KEs and KERs in the AOP-Wiki is being reviewed by the AOP-KB subgroup at OECD. It was noted that any suggestions from the CIAO crowd is highly appreciated.
The missing KEs identified by the groups included some neuro-related KEs, some KEs at different time points, additional details in the harmonized oxidative stress KE (NRF2-pathways and AngII-NOX links) and targets for recently approved drugs (eg: JAK-inhibitor corresponding to KE1282).

2.3.2 BO 2: **"**Ontology harmonization"

Goals
Ontology and terminology used in AOPs are critical parameters for building a comprehensive network. However, it has been noted that some KEs, KERs and AOPs lack harmonization within CIAO. The BO groups aimed at discussing how CIAO could efficiently work towards terminology harmonization at every level.

Report back and discussion
Controlled terminology is an area that the majority of CIAO participants are not familiar with. To improve ontology harmonization within the project, it was decided to set up a **CIAO ontology team**. In general, the tasks around ontology might be wide and ambitious to tackle. It was considered important to well define the scope of the new CIAO ontology WG, aiming for 'low-hanging fruits' and realistic objectives. The number of CIAO AOPs are 15 now, a number that makes it a good case study to explore the use of ontology based annotations. Small but effective changes could be proposed serving first the purposes of CIAO and possibly be extended and exploited beyond to the AOP-Wiki.

Regarding similar KEs, to assess how to choose the most appropriate decision, it was suggested to take the following factors into consideration: (i) Content - avoid KEs with little description, (ii) the connectivity, (iii) the temporal aspect, (iv) the essentiality and the measurability, (v) the terminology of the field, and (vi) if possible, merge KEs with different titles but similar meaning.

3. The meta-level aspect: What can COVID-19 research do for AOPs?

The AOP framework provides a platfrom for interdisciplinary and systematic gathering, organization and review of variable types of data and information across multiple levels of biological organization. Large scale AOP-aligned crowdsourcing has been limited to date. The current pandemic is a unique opportunity for implementation of wider community contribution into the AOP framework and can be expected to generate insight into further development needs of the AOP framework itself.

3.1 Results of the survey

A survey was launched among CIAO members in May to gather (i) the experience of CIAO members in participating in the CIAO project and (ii) the role of the AOP framework in the CIAO collaborative process. First the profile of CIAO members (expertise, work sector etc.) was compiled, then the interest and reasons for joining the project and the rewarding and challenging aspects were investigated. In the second part, the questions aimed to explore the role of the AOP framework, the AOP schematic/diagram and the AOP-Wiki platform within the CIAO collaborations. Around two-third of the CIAO crowd replied to the survey (45/66 - May 2021). The replies were presented and will be further analyzed in a coming publication.

3.2 Outputs of the meta-level workshop

As decided in the April workshop, a meta-level workshop was organized on the 30th of June 2021. The aim was to explore participants' experiences of the collaborative aspects of the project, and in particular, the role of the AOP approach in supporting the forms of collaboration necessary for CIAO. That is, collaboration with a high degree of interdisciplinarity, with contributions of knowledge from many different sources and disciplinary perspectives within a coherent framework. More than only bringing their piece of the puzzle, the project relies on that participants value how the pieces fit together. At the workshop, sub-groups of participants worked in BO groups to work through three sets of questions about how the AOP framework had mediated the CIAO collaboration, according to their experience and memory of the process. The three sets of questions related to: 1) the AOP framework as a conceptual scheme (that is, the main concepts and their inter-relationships), 2) the visual aspect of the AOP framework, that is diagrams and other schematics, and 3) the AOP-Wiki. While participants reported that they had come into the project with varying levels of understanding of the AOP framework, and that there are different kinds of challenges in adapting it for mapping the pathways of a viral disease such as Covid19, the framework itself generally did provide a sufficient anchor point and common framing that enabled discussions to be productive, and facilitated collaboration. The full results of the workshop will be described in a forthcoming paper.

3.3 BO group discussion

The level of details required within an AOP modelling COVID-19 have been raised in different WGs. It was proposed during this workshop to evaluate if the level of details should be appropriate to the use(s) identified for a specific AOP. Participants were divided in BO groups of +- 6 persons to discuss for an already developed CIAO AOP: the uses identified for this AOP, the current level of details and the potential additional information needed. The BO groups reported their discussion to the plenary.

BO 1. **AOP379** – *Increased susceptibility to viral entry and coronavirus production leading to thrombosis and inseminated intravascular coagulation*
Uses identified: Identification of knowledge gaps, communicating MFs, suggestion for policy (prediction of severe symptoms or adverse response of vaccination), development of therapeutics
Level of details: KERs need to be further developed.
Recommendations: KERs development, mapping of molecular regulation.

BO 2. **AOP392** - *Decreased fibrinolysis and activated bradykinin system leading to hyperinflammation*
Uses identified: Reuse, Knowledge gaps.
Level of details: Not clear, generic (broad reuse) or detailed (specific use)?
Recommendations: Interesting to think about broad application in order to solve 3R issues, connect medical to toxicological research, address reuse issues.

BO 3. **AOP412** - *SARS-CoV-2 infection leading to thromboinflammation*
Uses identified: Identification of new knowledge gaps; potential drugs target; opportunity to quantify role of thromboinflammation.
Level of details: the work is at the cellular level but finding a common ground in terms of level of details on the topic has been complex and working in compartments is not easy to define the best level of details.
Recommendations: important to consider the context and integrate evidence at a higher organizational level.

BO 4. **AOP320** - *Binding of viral S-glycoprotein to ACE2 receptor leading to acute respiratory distress associated mortality*
Uses identified: Framing the overall pathway from viral exposure to adversity and providing a structure to provide evidence for the adverse pathway to the lung; harmonization of CIAO language; identify potential therapies to repurpose for treatment
Level of details: The level of details of the pathway currently is sufficient from framing the main pathway of a major AO of the disease, however it is not detailed enough to identify biomarkers.
Recommendations: more specificity of inflammatory markers, coagulation, organ specificity and hyperinflammation processes are missing. Some KEs and KERs need to be fully developed; currently, the AOP in the Wiki does not match the diagram on the page, therefore a need was identified to continue to update pathways in this quick-moving field.

BO 5. **AOP394** - *SARS-CoV-2 infection leading to impaired olfactory function (anosmia)*
Uses identified: to help to establish diagnosis and to understand the relevance of anosmia and the prognosis for the patients, to help our mechanistic understanding of this clinical outcome of COVID-19 as a multisystem manifestations of the disease, to identify knowledge gaps.
Level of details. The level of details was considered as adequate to provide a better understanding of the mechanisms underlying anosmia in COVID-19 patients. The AOP captures well the details needed to help for diagnosis as it was developed with a clinician.
Recommendations. It was proposed that it could be relevant to describe the type of damage occurring to the olfactory sensory neurons.

4. The CIAO Ground rules

With CIAO now having more than 60 people collaborating, the coordination group felt that a series of rules need to be agreed upon which will govern the project work. The coordination group has therefore prepared and adopted a document called “CIAO ground rules” (available for download here: https://www.ciao-covid.net/groundrules) which was presented to the workshop participants.

The individual components of the CIAO project are:

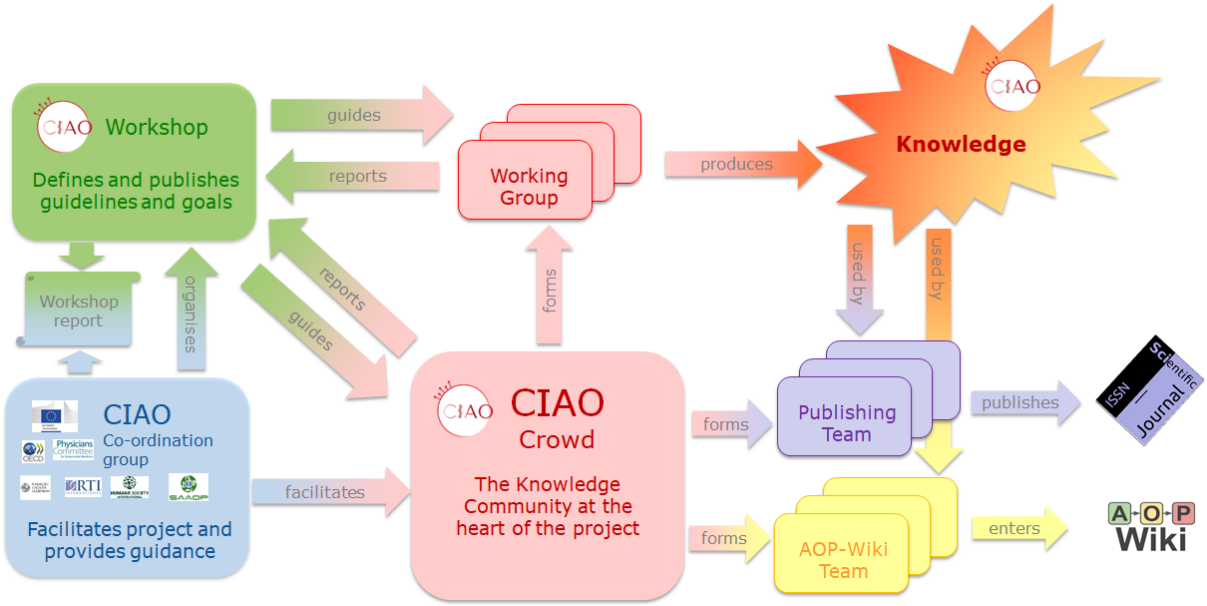

Figure 2. Individual components of the CIAO project.

The CIAO crowd is the knowledge community at the heart of the project. It forms working groups in which the actual scientific work of CIAO is executed, i.e. retrieval, review, assessment, arrangement and ultimately dissemination of the CIAO knowledge. In periodic CIAO workshops, the knowledge is presented and discussed, and the next steps are planned. The findings and decisions of the workshop are recorded in a workshop report (e.g. this document), which is prepared by the CIAO coordination group. The coordination group facilitates the work of the CIAO crowd, provides guidance and takes definitive decisions when needed. The CIAO crowd also forms publication teams and AOP-Wiki teams which - based on the CIAO knowledge - co-author journal papers or jointly enter knowledge into the AOP-Wiki. The Ground Rules also feature guidance on when the CIAO brand can be used, and introduces a conflict resolution mechanism.

All workshop participants (and in extension, all CIAO crowd members) were invited to explicitly acknowledge the rules at this link: https://forms.gle/Gw6XSJAwxxhPa3nx8.

5. Modulating factors (MFs) into the AOP framework

Identifying factors modulating the onset, progression and severity of the disease would help to understand why some populations are more vulnerable than others.

5.1 Challenges

MFs are mentioned within the AOP framework. The handbook (OECD, 2018) defines them as factors that alter the shape of the response-response function that describes the quantitative relationship between two KEs. In the AOP-Wiki they should be listed in the subsection "response-response relationship", along with relevant information regarding the manner in which they may alter the relationship. Only MFs with solid evidence, supported by relevant data and literature, should be listed. In practical terms, there is not much experience yet with MFs and the AOP framework.

Within the CIAO project, we identified several MFs with sufficient evidence for having an influence on the course of the disease. When trying to add this information to the AOP development, we faced some difficulties. The allocated space within the AOP-Wiki does not allow for entering more detailed information on MFs, like timeframe, mechanism, or multiple interactions. Besides, this descriptive text is not machine readable. In addition, the current definition of MFs should be questioned, because our findings show that MFs might also have a modulating effect on KEs. Further discussions, also with representatives from several OECD EAGMST (the steering committee of the OECD AOP development program) subgroups, are planned.

5.2 BO group discussions

A slido was proposed to the participants to select the MFs they would like to discuss. Based on the five most voted, five BO groups were formed.

BO 1: Sex
Ideally the probability to go from an upstream KE to the downstream KE should be described separately for men and women, with different colors for example or as a visible element in the graph. It was emphasized again that MFs should be described based only on evidence, not based on assumptions or correlations.

BO 2: Age
It is still not clear where to describe the differences between biological and chronological age. It was discussed if the differences related to age should be strictly restricted to measurable aspects or should be added only to KER within a table or adding links. It was identified that AOPs for children or developing organisms can differ, and that this aspect was not sufficiently considered so far within the project.

BO 3: Diabetes
Diabetes represents a biological factor linked to a pathological condition. Thus, diabetes could be depicted by AOP(s), sharing similar KE(s) with the COVID-19 ones, amplifying the magnitude of this/these common event(s). Jennifer Waspe and Merlin Mei have developed such putative diabetic AOP connecting with COVID-19 AOP392 at the inflammatory KEs. To

integrate diabetes within the COVID-19 AOP network, a co-morbidity sub-network could be drawn. The time aspect is also important to take into consideration. If COVID-19 patients develop diabetes following SARS-CoV-2 infection, then diabetes is an AO in the framework.

BO 4: Air pollution
Air pollution was proposed to modulate the clinical outcomes of COVID-19 either as a vehicle for the virus or by damaging the respiratory system, or possibly by modulating the inflammatory events. However further studies and mechanistic understanding are needed. Should air pollution therefore be considered as a pre-MIE factor, a MIE or a different AOP network was questioned.

BO 5: Genetic factors
Associating genetic variations with COVID-19 outcomes has been proposed by the Genetic and COVID consortium: https://www.covid19hg.org/. Most genetic variations do not seem to change the likelihood of the outcome, but the magnitude or severity of it. The impact of genetic variation seems to be different depending on the variants, questioning how the pathways, as described currently, are representative of the mechanisms following infection with the different SARS-CoV-2 variants.

6. Wrap up and ways forward

At the 4th CIAO AOP Workshop, the 15 AOPs depicting COVID-19 outcomes already entered into the AOP-Wiki were assembled into a preliminary COVID-19 AOP network. Controlled vocabulary, training on KER development and integration of the MFs into the AOP-Wiki were identified as next steps needed to consolidate the various single AOPs and the network.
The plenary then agreed that, until the next CIAO workshop which will take place in March 2022, the current WGs will consolidate AOPs/KEs, develop further KERs and implement MFs (Table 2). Zoom-in publications will be drafted. The network team will pursue building the network based on the AOPs developed within CIAO. Training workshops will be organized related to KER development and ontology harmonization.

Table 2. Next steps for CIAO

	Next steps	Timing
WG tasks, zoom-in publications	Consolidation of AOPs/KEs/KERs within the WGs	March 2022
	Implement integration of the MFs	March 2022
	Neuro WG: anosmia and network papers– 1st draft	November 2021
	MF WG: MF in COVID-19 AOP paper – 1st draft	December 2021
	Literature review – protocol publication	To be defined
	Multiscale approach	To be defined
	Meta-level aspect	To be defined

CIAO AOP network	Preliminary network sent around for feedback	October 2021
	AOP network publication – 1st draft	December 2021
Workshops	Training workshop on Weight of Evidence in KER	12 November 2021
	Training/webinar on ontology	To be defined
	5th CIAO AOP Workshop	9-10 March 2022

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Annex A. Participant list.

First Name	Name	Organisation	Country
Alan	Hargreaves	Nottingham Trent University	United Kingdom
Alberto	Mantovani	National Health Institute of Italy	Italy
Alicia	Paini	Joint Research Centre of the European Commission	EU
Amalia	Munoz-Pineiro	Joint Research Centre of the European Commission	EU
Ann	Lam	Green Neuroscience Laboratory, Neurolinx	United States of America
Anna	Beronius	Karolinska Institute	Sweden
Annamaria	Carusi	Interchange Research Ltd	United Kingdom
Brigitte	Landesmann	Joint Research Centre of the European Commission	EU
Catharine	Krebs	PCRM	United States of America
Christos	Andronis	Biovista	Greece
Clemens	Wittwehr	Joint Research Centre of the European Commission	EU
Daniel	Jacobson	Oak Ridge National Laboratory	United States of America
Donna	Macmillan	Human Society International	United Kingdom
Eftychia	Lekka	Biovista	Greece
Elan	Ohayon	Green Neuroscience Laboratory, Neurolinx	United States of America
Elma	Omeragić	University of Sarajevo-Faculty of Pharmacy	Bosnia and Herzegovina
Felicity	Gavins	Brunel University London	United Kingdom
Gillina	Bezemer	Impact Station (also Uni Utrecht)	Netherlands
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Annex B. CIAO AOPs and KEs in the AOP-Wiki

Hub AOs

AOP379	Increased susceptibility to viral entry and coronavirus production leading to thrombosis and disseminated intravascular coagulation
AOP392	Decreased fibrinolysis and activated bradykinin system leading to hyperinflammation
AOP412	SARS-COV-2 infection leading to thromboinflammation

Lung AOs

AOP320	Binding of viral S-glycoprotein to ACE2 receptor leading to acute respiratory distress (ARDS) associated mortality
AOP377	TLR9 activation leading to ARDS and Multi Organ Dysfunction
AOP173	Substance interaction with the lung resident cell membrane components leading to lung fibrosis
AOP319	Inhibition of Angiotensin-converting enzyme 2 leading to lung fibrosis
AOP302	Lung surfactant function inhibition leading to decreased lung function
AOP382	Angiotensin II type 1 receptor (AT1R) agonism leading to lung fibrosis

Neuro AOs

AOP374	Binding of SARS-CoV-2 spike protein to ACE2 receptors expressed on brain cells leads to neuroinflammation resulting in encephalitis
AOP394	SARS-CoV-2 infection leading to impaired olfactory function (anosmia)
AOP395	Binding of SARS-CoV-2 spike protein to ACE2 receptors expressed on pericytes leads to intravascular coagulation resulting in stroke

AOP381	Binding of viral S-glycoprotein to ACE2 receptor leading to dysgeusia

Other organs AOs

AOP383	Inhibition of Angiotensin-converting enzyme 2 leading to liver fibrosis
AOP422	Binding of SARS-CoV-2 to ACE2 in enterocytes leading to GI disorders

Viral entry, replication and ACE2 related KEs.

KE1738	Susceptibility to viral entry, increased
KE1739	ACE2 binding to viral S-protein
KE1847	Coronavirus production, increased
KE1901	Interferon-I antiviral response, antagonized
KE1854	ACE2 dysregulation
KE1740	ACE2 inhibition
KE1787	ACE2 downregulation
KE1752	Angiotensin II, increased
KE1851	Binding of agonist, Angiotensin II receptor type 1 receptor (AT1R)
KE1852	Increased Ang II type 1 receptor (AT1R)

Inflammation, ROS or thrombosis related KEs

KE1492	Tissue resident cell activation
KE1493	Increased pro-inflammatory mediators
KE1494	Leukocyte recruitment/activation
KE1496	Increased, secretion of proinflammatory and profibrotic mediators

KE1497	Increased, recruitment of inflammatory cells
KE1750	Increased inflammatory immune response
KE1842	Prolonged TLR9 activation
KE1848	Toll like receptors, dysregulation
KE1706	TLR7/8, simulation
KE1844	Systemic inflammatory response syndrome
KE1868	Hyperinflammation
KE1857	Neutrophil-platelet interactions, increased
KE1392	Oxidative stress
KE1115	Increased, reactive oxygen species
KE1869	Oxidative stress response
KE1866	Fribinolysis, decrease
KE1867	Bradykinin system, activated
KE1845	Coagulation
KE1846	Thrombosis and disseminated intravascular coagulation
KE952	Blood pressure, increase
KE1375	Platelet aggregation
KE1678	Impaired oxygenation of the blood
KE1501	Increased, extracellular matrix deposition
KE68	Accumulation Collagen

KE1825	Cell death
KE351	Increased mortality

Lung AOs

KE1498	Loss of alveolar capillary membrane integrity
KE1458	Pulmonary fibrosis
KE1276	Lung fibrosis
KE1672	Inhibition of lung surfactant function
KE1748	Increase, the risk of acute respiratory failure
KE1843	Acute respiratory distress syndrome (ARDS) and multi organ dysfunction

Neuro AOs.

KE188	Neuroinflammation
KE352	Neurodegeneration
KE1841	Encephalitis
KE1870	Sustentacular cells, decreased
KE1871	Olfactory sensory neurons, decreased
KE1872	Olfactory epithelium degeneration
KE1873	Impaired olfactory function (anosmia)
KE1874	Blood brain barrier disruption
KE1875	Cerebrovascular disease (stroke)

Other organs AOs.

KE902	Inflammation, liver

KE1549	Liver injury
KE709	Increase, cytotoxicity (renal tubular cell)
KE814	Occurrence, Kidney injury
KE1535	Heart failure
KE1043	Hypertrophy/hyperplasia (heart)
KE1931	Increase, intestinal permeability
KE1932	Gastrointestinal disorders