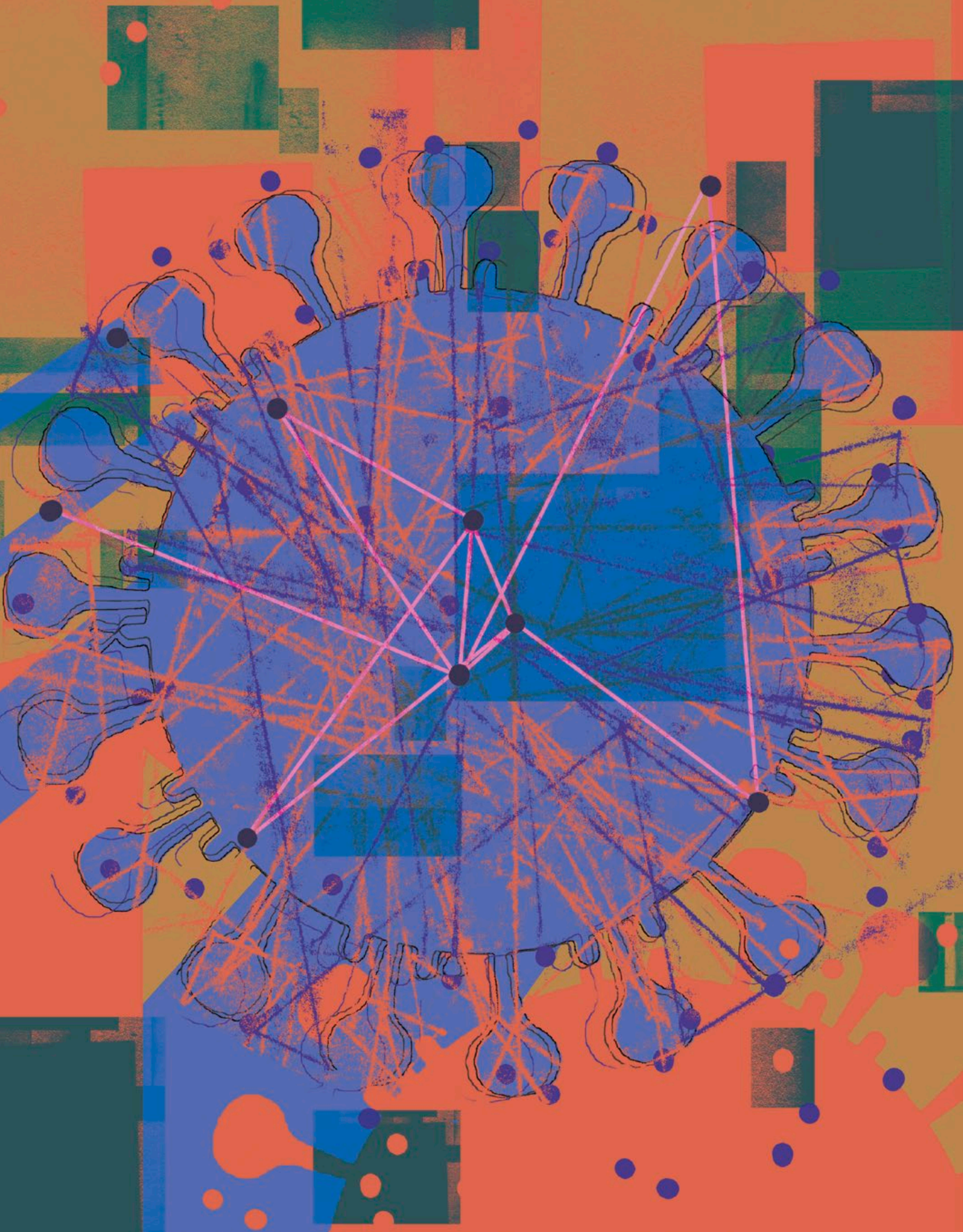


ANNAMARIA CARUSI, LAURE-ALIX CLERBAUX, AND CLEMENS WITTWEHR

How to Catalyze a Collaboration

When an interdisciplinary, international group of researchers turned their attention—and a tool for knowledge structuring—to work out the mechanisms of COVID-19, they learned how diverse scientists can synthesize information constructively.

In the early months of the pandemic, researchers working to respond to the urgent need for information were faced with constraints on conventional collaboration. In an attempt to address both problems at once, we—a scholar of scientific collaboration and managers of a European effort to assess chemical safety—helped start a group to do interdisciplinary research on COVID-19. In less than three years, we grew from casually tweeting to publishing 11 studies and engaging about 80 researchers across 20 countries. Together we worked to puzzle out more than a dozen mechanisms by which the virus causes harmful effects, such as loss of smell and respiratory failure, all uploaded to an open access platform. What enabled this effort to succeed was our use of a shared approach and collaborative platform—a scaffold for assembling information—that demands precision, accommodates social complexity, and builds bridges across disciplines.

Our collaboration grew out of an existing project at the Organisation for Economic Co-operation and Development (OECD) called the Adverse Outcome Pathway (AOP) program, which coordinates research to help predict whether commercial chemicals will have toxic effects on humans or the environment and what those effects might be. Adverse outcome pathways use predefined schema to depict the series of molecular, cellular, or physiological events whereby a chemical causes harm. The AOP program supports toxicologists working in regulatory agencies to assess whether cosmetics, food, feedstuffs, and industrial chemicals might cause toxicity, providing a way to move away from animal testing. For example, AOPs describing how chemicals can lead to skin irritation have been crucial to regulatory changes in Europe, in one instance retiring a test for skin sensitization that required exposing test animals to potential toxins, usually by rubbing them on shaved hamsters or rabbits. To wit, understanding the mechanisms behind toxicity enabled better ways to deal with it.

In early 2020, the mechanisms of SARS-CoV-2 were unclear. What cells did the virus access? How did infection lead to excessive inflammation or respiratory failure? All of these questions had a core component: What were the biological pathways by which the virus caused disease?

Penny Nymark, a toxicologist at Karolinska Institutet and a contributor to the AOP program, proposed building on our existing toxicology framework to understand the pathway of events leading to infection and disease. It started, of course, on Twitter, with a tweet from Nymark: "Figured I'd do my bit in the ongoing crisis to build an AOP-linked #WikiPathway for Covid-19 #covidpathways Why a tox-focused #AOP for virus-infection, you ask? Well, it turns out the disease that follows is not so different from particle-induced lung injury."

Soon afterward, Maurice Whelan, head of the European Commission's Joint Research Centre (JRC) Unit for Systems Toxicology, replied enthusiastically, tagging one of us (Wittwehr) who works in the same unit and is heavily involved in the AOP program.

Illustration by Shonagh Rae

Thus was born CIAO (Modelling COVID-19 Using the Adverse Outcome Pathway Framework). The acronym was chosen to convey the eagerness of the team, partially based in Italy, to say *ciao!* to COVID.

In giving the go-ahead for his JRC unit to host and coordinate the project, Whelan noted that "the process is as important as the output." Consequently, CIAO included self-reflection from the outset. This was made easier by the fact that one of us (Carusi) is a specialist in the study of scientific processes, particularly on how routines and scaffolds can support shared understanding and illuminate differences.

How AOPs work in toxicology

The AOP framework is a way to organize information about each step of a pathway from an initial event (for instance, a particular allergen found in latex gloves binds a receptor on a specific sort of immune cell on skin) to an adverse outcome (an itchy rash). It's a bit like naming the first and last domino in a chain—plus all the dominos in between—and specifying what key events along the pathway make each domino fall down. This pathway approach shows *how* an adverse outcome happens, not only *that* it happens. Figure 1 shows how it is normally rendered.

The AOP approach is simultaneously scientific and social. Scientific because it provides a conceptual vocabulary and grammar (logic) to explain mechanisms; social because it brings scientists together in ways that allow them to collaboratively fill in information. The AOP framework is also inherently interdisciplinary because toxicity pathways cut across biological levels and therefore across disciplinary silos, from proteins to cells to whole organisms. This framework is the backbone of the AOP-Wiki, a platform for sharing knowledge: researchers can submit an AOP to the platform, which can then be seen and commented on by other members. It currently holds more than 400 AOPs, with 256 of them recognized officially on the "OECD workplan." It is both a publishing platform and social media connector, originally modeled on crowd-sourced sites like Wikipedia. The community of developers and users has grown from a handful of early adopters in 2012 to over 800 (with 300 of them having editing privileges) in 2023. CIAO members soon became a part of this community.

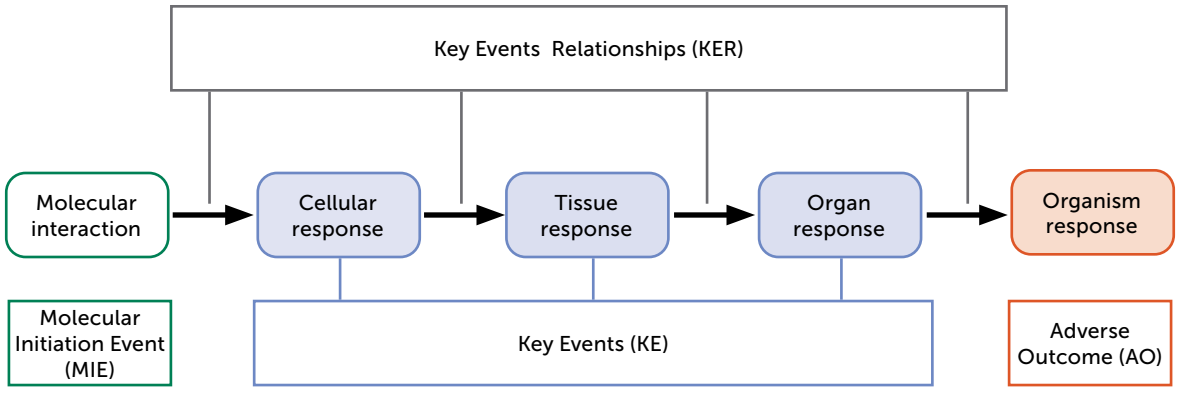
Expanding the AOP-Wiki for COVID-19

To build a community around COVID-19 pathways, Wittwehr called for collaborators over social media and by word of mouth. Participants were encouraged to invite anyone they thought had something to contribute. It quickly became clear that CIAO's mission resonated with the research community. In fact, a survey of participants a few months after launch showed that the chief motivation for joining was the desire to be part of an interdisciplinary collaborative effort, followed closely by the desire to contribute to the understanding of COVID-19. The commitment of participants did not flag as the project evolved. Meetings soon had too many participants and too many topics.

At the first online workshop in early October 2020, more than 40 people filled the Zoom screen. To make collaboration practical, we divided into working groups based on the timeline of pathogenesis (for instance, early events such as infection or late events such as respiratory failure) or type of event (inflammation or not), which helped give people a "home" within the project.

The working groups were free to decide which AOPs they would work on and when and how their meetings would occur. Normally they were held every four to six weeks, with members doing much of the work in between meetings. All meetings were preceded by an agreed-upon agenda and followed by approving the minutes. Around two-thirds of the participants were in more than one working group.

Figure 1. THE ADVERSE OUTCOME PATHWAY FRAMEWORK



As the working groups took off, the nucleus of CIAO founders transitioned to a formal steering committee, adding a few other dedicated, insightful participants who we co-opted. This committee, which included representatives of each working group, met twice monthly, helped harmonize terminology, arranged training, and identified cross-cutting opportunities. The project overall maintained focus by holding workshops across all working groups twice a year and organizing coauthored publications. A newsletter also kept participants apprised of the AOPs stacking up, work in progress, and new developments.

Getting the organizational structure right was crucial. One of us (Clerbaux) was employed by JRC as a project manager and became the primary point of contact for the project. Having a dedicated individual to knit together the group both socially (communicating, organizing, keeping track of tasks and logistics) and scientifically (seeing the connections between different working groups, adding expertise on particular aspects) sustained momentum and kept the project moving forward. Clerbaux took to describing her own role with an apt biological metaphor: "Coordinating such an interdisciplinary project is like acting as an enzyme—when all reagents are present together, it is catalysts that push the reactions to happen."

The ethos of the project from the outset was to be open to anyone with relevant expertise. The community grew through a snowball effect, with participants recruiting additional experts. We also advertised the CIAO workshops broadly, hoping to share what we had achieved so far and recruit others. Acceptance and inclusion into the crowd was enthusiastic and informal.

As our population and productivity grew, we ran into a situation where one participant objected to being a coauthor with someone affiliated with a tobacco company, especially with smoking being a factor in making the disease more deadly. This prompted intense conversations and soul-searching, including a publication delay of several months. We realized our ethos for the project had been implicit rather than explicit. Eventually, we set up distinct criteria for inclusion in the crowd and for inclusion on author lists. We also established ground rules clarifying expectations and laying out how to resolve conflicts. From then onwards, the sheer existence of the document seemed to help to overcome potential bumps in the road.

Reworking the working groups

As the pandemic went on, it became increasingly obvious that COVID-19 attacks many organs, so the working groups were reshuffled accordingly. At this point, many participants were not familiar with AOPs. They had to see whether their knowledge could fit within the schema of the AOP framework. At the same time, the participants pushed, prodded, and adapted the AOP framework itself in a true two-way dialogue between the knowledge framework and those applying it.

These conversations produced two new working groups, neither of which we would have imagined within the original AOP approach. One group focused on modulating factors known to influence the outcome of disease, including sex, age, comorbidities, and lifestyle, all of which provide crucial context for disease mechanisms and should be considered for their effects on various pathways. The other working group dubbed itself the "rogue" group (also called the multiscale group). It sought a more holistic view that incorporated socioeconomic factors and questioned even the biological basis of the AOP default, in which an outcome is initiated by a molecular event. Even while efforts advanced particular AOPs, there were many overarching discussions and debates, with opportunities to share progress—and challenges—at regular meetings and workshops.

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Self-reflections

One of us (Carusi) and a small meta-level group took on the explicit task of self-reflection to learn as much as possible about how the CIAO collaboration worked. We queried participants about the AOP framework's concepts and definitions, its diagrams, and its wiki. We wanted to know whether this approach supported interdisciplinary collaboration effectively and how well it could extend from its original territory of toxicology to infectious disease.

One participant eloquently captured the lack of shared language, ontologies, and vocabulary—usually the biggest challenge to interdisciplinary collaboration: *Sometimes we*

talk about the same thing but it's called differently, or the other way around.

This is where the AOP framework acts as a scaffold to support conversations across disciplines. The work to fit knowledge into the concepts and definitions of the framework, and to order events and relationships in the diagram, structures collaboration. At a minimum this provides a way of identifying where misunderstandings occur, if not an immediately shared vocabulary and grammar. It can also allow implicit perspectives and even biases to be brought to light:

> *How to use the framework makes you constantly think and reflect, on your own ideas and perhaps also your own biases.*
>
> *Even though you don't always agree, these conversations make you think in a different way.*
>
> *When you start visualizing these things, you start to see how other people are viewing things.*

This can bring about profound new perspectives. Here is a (lightly edited) excerpt from an interview with two participants who had worked together on an AOP:

> **Virologist:** *We'd ask each other, "So how does it work in your system? How does it work in my system?" And then we'd draw out parallels between the different systems and try to make things work. And for me, I actually learned a lot, especially in terms of how you can discuss things that can complement the discussion.*
>
> **Toxicologist:** *Yeah, and you learn from taking in this new information that you don't necessarily fully understand. But you understand that there's a different view of what you thought was truth. And then you learn how you can apply it to making your own truth better, basically.*

They went on to talk about the moment each realized there were specific parallels and differences between a virus and a chemical as stressors, an understanding that would not have been obvious without the framework. The excitement of the discovery was palpable; it was clearly a joyful moment that satisfied scientific curiosity and spoke to their core reasons for being scientists. This was compounded by the collaborative nature of this discovery, in a kind of scientific unity with another person—the very opposite of an individualistic competition.

There were many more dialogues generating substantive new insights through the framework. One of the most intriguing was how the framework itself expanded to capture modulating factors as it extended from toxicology to apply to infectious disease. As one participant recounted:

> *This idea of modulating factors is fundamentally a serious problem because there is a continuum between what we call an event and a modulating factor. And things that we think are events, sometimes, especially if you think about COVID … things that are modulating factors can mean the difference between ... life and death.*

We like to think of the AOP approach as providing a metaphorical campfire around which people from different disciplines can assemble and construct knowledge. Once that expertise is assembled, the collective goal of filling out the pathway is an essential catalysis that crystallizes knowledge.

However, the success of the project cannot be solely attributed to a framework. It was a unique time; many scientists could no longer go to their labs and workplaces and were eager to be of use. About half of our participants were from academia, with the rest from companies, nongovernmental organizations, and public institutions. The CIAO members were highly motivated volunteers more interested in producing information than receiving individual credit. Our survey also revealed that 62% of participants were women, and an even higher percentage held senior roles in their institutions. In contrast, women make up about 50% of the life sciences workforce. Perhaps CIAO bears out a 2007 analysis by researchers Diana Rhoten and Stephanie Pfirman suggesting that women are more likely to participate in interdisciplinary collaborations. What was abundantly clear was that a large group of people from different scientific and cultural backgrounds could collaborate effectively with the help of a knowledge assembly framework they could embrace.

We think our experiment in interdisciplinarity shows a certain set of necessary conditions for successful collaboration: scientists whose motivations to collaborate override individual gain; a coordinated, flexible, and sustained organizational structure; a framework designed to allow different perspectives to be acknowledged; and a shared language to evolve. We hope that the process we lived through can be an inspiration for others.

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