ANALYTICAL RESEARCH INFRASTRUCTURES IN EUROPE

VIRAL AND MICROBIAL THREATS

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ANALYTICAL RESEARCH INFRASTRUCTURES OF EUROPE (ARIEs) JOIN FORCES TO FACE THREATS SUCH AS COVID-19 AND OTHER POSSIBLE FUTURE CRISES

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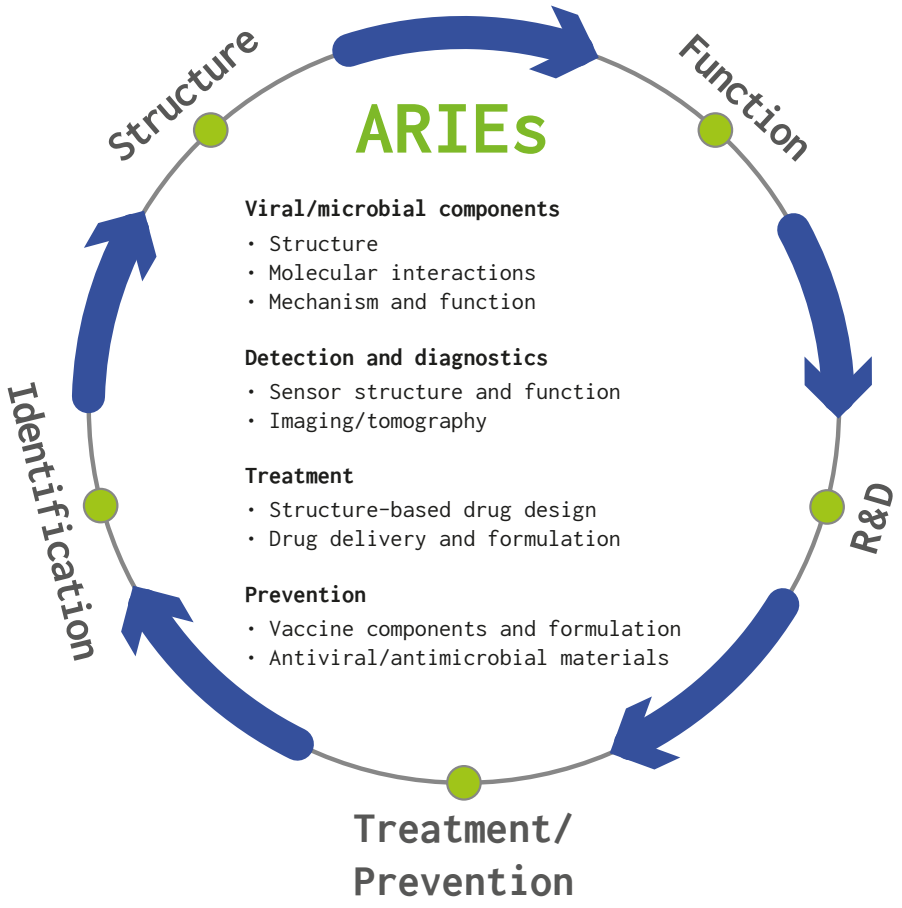
TABLE OF CONTENTS

AT A GLANCE

The Analytical Research Infrastructures of Europe (ARIEs) provide unique windows into the workings of the world around us. ARIEs include powerful photon sources, such as synchrotron storage rings, laser systems and free-electron lasers; sources of neutrons, ions and other particle beams; and facilities dedicated to advanced electron-microscopy and high magnetic fields. In 2020, the varied and complementary analytical techniques of ARIEs, coupled with the strong scientific networks established in Europe, have made it possible to coordinate efforts to combat the unexpected challenges of the COVID-19 pandemic.

ARIEs are centres of scientific and technological excellence, delivering services, data and know-how to a growing and interdisciplinary user community comprising more than 40,000 researchers in academia and industry across a wide range of domains: life science, the physical sciences, energy, engineering, the environment and the earth sciences, as well as medicine, health, food and cultural heritage. Access to the ARIEs by the scientific user community is free and peer reviewed, based upon the principles of scientific excellence and open data. This paper describes how the ARIEs have responded rapidly to Covid-19, as well as how they will address the scientific and operational challenges posed by the pandemic and future viral or microbial threats. The impact of the ARIEs results from the complementarity of their unique individual analytical techniques, which, in combination, provide unmatched analytical capabilities to study infectious diseases. It ranges from investigations at near atomic level (required for understanding the molecular mechanisms of infection and the structure-based design of antimicrobial and antiviral therapeutics) to developments in detection, treatment and prevention.



Life Science and Medicine

- Viral genome
- Viral/microbial lifecycle
- Pathology of infection
- Target identification
- Cell assays
- Animal models
- Drug discovery/bioprospecting
- Benchmarking
- Target validation

Industry

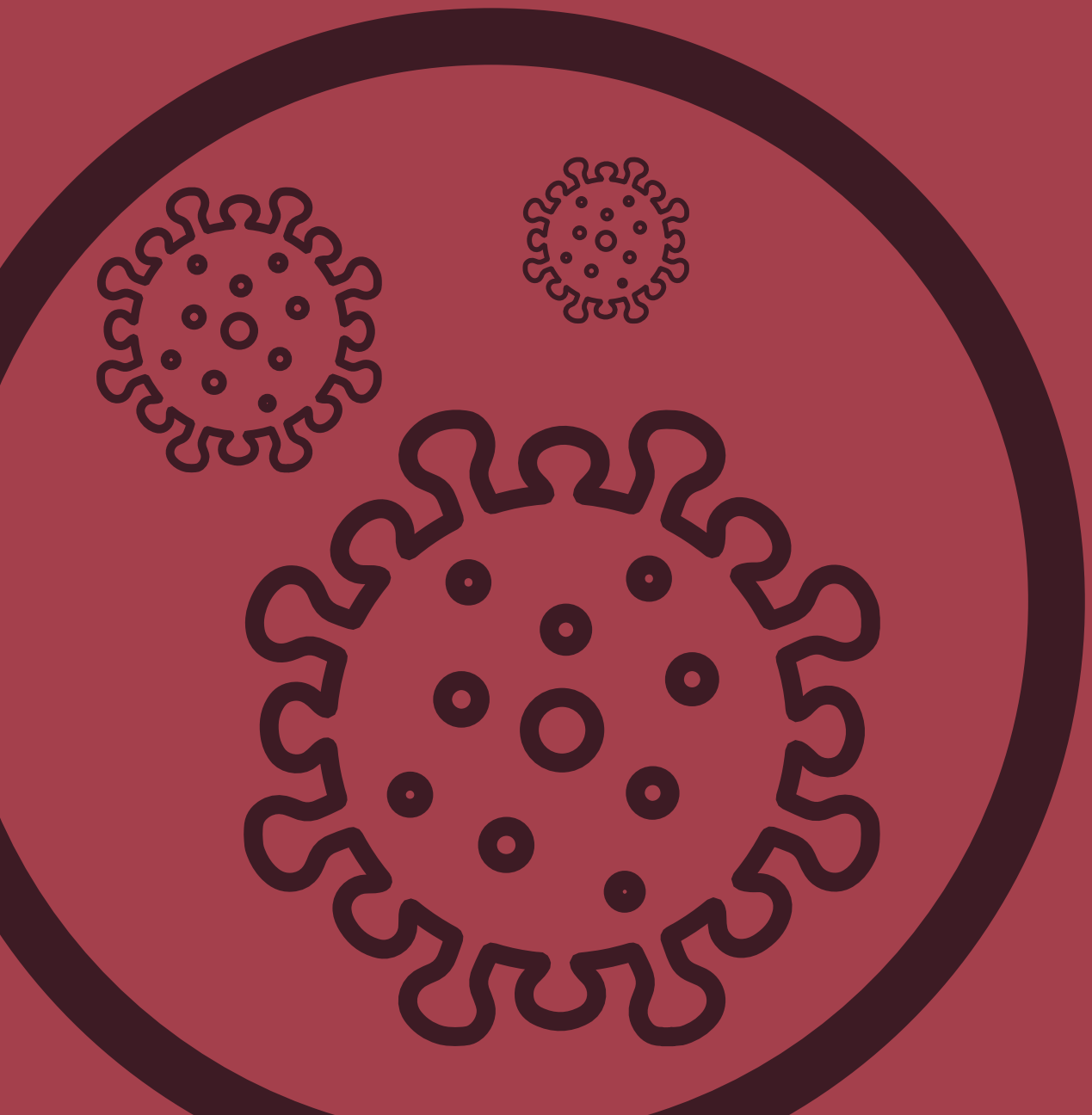
- Drug/vaccine development
- High throughput screening
- In vitro assays
- Drug delivery and formulation
- Clinical trials
- Test kits
- PPE
- Antiviral/microbial materials

The technical expertise of the ARIEs has an impressive track record in fostering the development of critical technologies for diagnostic and/or therapeutic procedures in medicine and health. These include hadron therapy, the development of radiopharmaceuticals for diagnosis and therapy, magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon-emission computed tomography (SPECT), all of which are in widespread use. In addition, structural biology, which has so far predominantly been performed using X-ray sources, provided invaluable information on the interaction of drug molecules with their biological targets and laid the foundation for structure-based drug discovery. More recently, novel X-ray imaging technologies have been developed at the ARIEs with important potential clinical applications. While most technologies have been developed for detection and treat-

ment of cancerogenous tissue, they can also be adapted to directly or indirectly detect infectious agents. Looking ahead, there is in particular an urgent need for technologies that can be quickly adapted to new pathogens, and that are able to detect them in the environment at low cost.

The combination of high-end infrastructure and expertise at the different ARIEs is unmatched in the world and forms an ideal base to develop new and existing multi-disciplinary approaches to tackle infectious agents. For this to be successful, however, there must be funding and networking possibilities to enable international teams of experts from the medical and biomedical-research communities to collaborate more closely, and sustainably, with ARIE scientists and engineers. Bolstered by the health cluster of Horizon Europe (HE), it presents an unprecedented opportunity to deploy the ARIEs' unique combination of analytical techniques, skills and know-how to efficiently target viral and microbial threats. The result will be an acceleration both in research that combats viral and microbial threats, and in the development of fast in-field testing capacities and other solutions to protect the health of Europe's citizens.

VIRAL AND MICROBIAL THREATS



1. THE CHALLENGE

The sudden emergence of new infectious agents with no known cure has been a major threat to human civilization throughout history. Fortunately, a much better understanding of the biology of infectious diseases, coupled with the development of vaccines and the discovery of antibiotics, has allowed the control or eradication of many historically challenging diseases. However, evolutionary pressure will inevitably lead to the emergence of new pathogens that evade current modes of prevention or treatment. Examples from the more recent past include bacteria such as the Methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant tuberculosis strains and EHEC E.coli, prion-based infectious diseases, and viruses such as HIV, Ebola, Zika and the new coronaviruses SARS-CoV and SARS-CoV-2. It has been surprisingly challenging to develop therapies and/or vaccines for these infectious agents, meaning that most of the above-mentioned examples are primarily kept under control with public health measures, such as improved awareness of proper hygiene. The main challenges when dealing with novel infectious agents are the:

1. rapid emergence of the infectious agent, and an unpredictable duration of epidemics/pandemics;
2. limited diagnostic and testing capabilities;
3. lack of proper detection of the infectious agent in the environment, in particular for rapid screening of surfaces and the air;
4. lack of effective therapeutics for affected individuals with severe symptoms;
5. lack of preventive agents, in particular vaccines.

The sudden emergence of the SARS-CoV-2 virus and the associated COVID-19 disease has unambiguously placed the vulnerability of human society to novel pathogens in the spotlight. It has also highlighted the tremendous economic impact that novel diseases can wreak even though the lethality of COVID-19 is, by the standard of historic pandemics, moderate. Moreover, the unpredictability of the emergence and disappearance of novel infectious agents makes it highly challenging for commercial entities to commit substantial investments to the development of specific diagnostics, drug or vaccines. Public bodies such as the EC, which are able to afford long-term investments in possible future public-health threats, are best placed to fund the tackling of novel pathogens and prepare for future pandemics strongly and efficiently. In addition, the spread of infectious agents has never been – and most likely never will be – stopped by invisible political barriers such as borders, and are therefore inherently a highly international, even global, challenge defying local strategies.

In rapidly confronting an emerging infectious agent with new diagnostic, treatment and prevention methods, the role of cutting-edge fundamental research into that agent's structure, molecular function and pathophysiology cannot be understated. However, in order to take the results all the way from "bench to bedside" requires close collaboration between multidisciplinary teams and organisations. As centres of scientific and technological excellence, the ARIEs drive world-leading fundamental, applied and industrial research and form an essential link in the research-and-innovation chain with their unique insights into the function of both living matter and materials. They are also constantly redefining the state of the art in technology.

2. REACTION OF ARIEs TO COVID-19

The current SARS-CoV-2/COVID-19 pandemic caused a worldwide emergency with no precedent in recent history – we have to look back to the 1918 influenza (the so-called "Spanish flu") for any comparable crisis. The ARIEs have been addressing this challenge by quickly overcoming the challenges of operation under social-distancing measures while making themselves available to those researchers who are seeking to study the novel virus and its effects. Dedicated rapid-access programs for COVID-19 research were immediately initiated by several of the ARIEs (see e.g. https://www.esfri.eu/covid-19; https://lightsources.org/2020/08/27/lightsource-research-and-sars-cov-2/). These have allowed scientists to develop innovative methodologies for pathogen detection and therapy, and to better understand the effect of COVID-19 on lung tissues. Meanwhile, the protein-production capabilities at the ARIEs have directly supported blood-serum and structural studies, providing key insights into virus-host interactions. First results are already in the public domain (see achievements section below), clearly illustrating the importance of ARIEs in overcoming the pandemic. However, finding ways to operate large scale research infrastructure with limited or non-existing user mobility, under the required special safety access conditions was not without its challenges. The lessons-learned and the demands ahead are summarized here.

OPERATION OF ARIEs DURING THE COVID-19

The ARIEs play a crucial role in facing some of the biggest fundamental scientific and societal challenges of our time. They have swiftly stepped forward to allow continuous operation during the current COVID-19 pandemic. While much human activity stopped as COVID-19 swept from one country to the next, the ARIEs had to adapt to the constraints of operating in a post-COVID-19 world by ensuring that they could provide their essential services for studies of the virus safely and reliably, and, longer term, provide facilities for a much wider range of research. During the crisis, the ARIEs focussed on minimising risks to the safety of staff and users, while expanding their range of remote services for a user community that will probably face travel restrictions for as long as the pandemic continues. By supporting SARS-CoV-2 research during national lockdowns, the ARIEs provided the infrastructure, which made it possible to obtain critical insights into the structure and function of the virus – insights that will likely prove indispensable for the understanding of the disease and the development of vaccines. They have already contributed to a first understanding of the physiopathology of the virus on lung tissues in the most severely affected patients.

a. Safety

The response of each of the ARIEs was very different, being influenced by its home country. Unsurprisingly, activities were much more constrained in countries with longer, more restrictive lockdowns. Nevertheless, many ARIEs established as quickly as possible support for COVID-19 research with the introduction of clear working protocols and the universal adoption of remote user-access. Most facilities also set up controlling-emergency boards. The internal decisions made in these boards ensured that all safety measures required by government authorities were implemented and followed. Safety measures for facility staff, for example, included the safe occupancy of working

areas and movement between them; meanwhile, social distancing (1.5 to 2m) and, in most cases, PPEs usage were guaranteed in all public spaces (meeting rooms, cafeterias, etc).

b. Remote Access

Depending on the size of their facilities, their experiment teams, the complexity of their set-ups and their prevailing operational status, some ARIEs could react faster than others in implementing remote-access protocols for COVID-19 research. Generally, critical services not requiring user access, such as deuterium-labelling and crystallisation platforms, were made available as soon as considered safe. But while the emergency situation highlighted the strengths of the ARIEs – such as their immediate response to the needs of sectorial research, and their flexibility to adapt to extraordinary working conditions while maintaining essential operations and scientific progress – it also exposed a number of weaknesses. In particular, while remote access to facilities for macromolecular crystallography (MX) is relatively well-established, it is not so for related areas of science such as medicine and biomedicine. Issues that will have to be addressed in the near future to implement or improve inter-facility remote access to non-MX, and in some cases MX-based, ARIEs technologies in these scientific communities include:

- potential re-developments of beamlines and processes;
- further development of critical sample-preparation facilities, such as deuterium-labelling and crystallisation platforms, to enable a rapid response to new research targets;
- greater degrees of automation; i.e. more robotics and standardised sample environments, where possible;
- standardised holders to enable shipping and straightforward robotic mounting of samples;
- development/improvement/standardisation of data acquisition, analysis and management software;
- development and enhancement of workflows;
- computational support and cybersecurity;
- access to the facilities themselves, particularly the rethinking of scheduling processes and culture;
- training of users in remote-access protocols, including transport of samples to/from ARIEs.
- increasing staff resources

c. User Support

The operation of ARIEs during the pandemic has also highlighted the need to provide enhanced levels of staff-assistance in experiments. This is particularly the case for experiments with non-standard set-ups, and for those which cannot be efficiently carried out currently via remote control. Communication and interaction with users were inevitably strongly hampered by the extraordinary working conditions. The immediate response to the emergency included the rapid set-up of a number of tools for interaction between facility operators and users (video conferences, remote offices, etc). Again, despite being effective and mostly very efficient, however, these tools could not:

- be an equal substitute for face-to-face interactions, in particular when breakthroughs were targeted;
- allow teams within large international collaborations to share their specific technologies and know-how as effectively as they could on site;
- solve complex experimental issues as fast, and thereby ensure the same chance of experimental success, as when there was physical proximity;
- share workloads, diverse experiences and expertise as users do on site, to promote positive, creative and innovative outcomes;
- guarantee the same pool of available candidates for staff positions, as users, and particularly young scientists, were not closely involved with facility operations.

Out of every crisis, however, there is a new opportunity for growth and innovation. The ARIEs' working group is committed to view these exceptional times as such an opportunity. Already possible solutions have been identified, such as the development of new operational tools for remote access, the standardisation of hardware and software, including communication tools, and the establishment and codification of protocols to allow safe user access to the facilities as soon as travel is possible.

3. ACHIEVEMENTS

The global race for detection, widely available testing and diagnostic tools, as well as a vaccine and therapeutics for COVID-19, requires more than genetic information. Modern analytical tools found at the ARIEs such as synchrotron X-ray radiation, cryo-electron microscopy and neutron scattering are required to gain atomic-level information about a virus's structure and functionality; in turn, they shed light on its biological and physiological processes, such as its adhesion to human target cells and its replication at a molecular level. Determining the atomic-level structure and function of a virus, therefore, is one of the first lines of investigation for the development of therapies.

Indeed, the combined use of X-ray/neutron crystallography and cryo-electron microscopy/tomography provides an atomic-level insight not only into the structures of individual viral proteins, but also into higher-order protein-protein complexes, which are crucial to the life cycles of viruses and other pathogens. Disrupting the mechanisms of action of individual proteins or the formation of higher-order protein-protein complexes with pharmaceutical drugs is one possible route for the therapeutic treatment of pandemic diseases. For this reason, researchers are seeking structural information on complexes of drug-targets and potential inhibitors, to speed up the process of drug and vaccine development for COVID-19.

Major discoveries on the SARS-CoV-2 structure performed by European groups in the ARIEs have been released in high impact scientific journals, and shared with the scientific and medical community, since the beginning of the COVID-19 crisis. For example, cryo-electron microscopy allowed the determination of the structure and the dynamics of the SARS-CoV-2 "spike" protein that anchors the virus to the surface of a human cell. These studies revealed an unexpected flexibility in the spike, which might help the virus scan the cell surface in search of a receptor for entry. Meanwhile, X-ray crystallography revealed the conformation of several so-called non-structural proteins, including key enzymes involved in the virus's replication. The structure of the virus was studied via isolated viral particles, but also directly within infected cells by cryo-electron tomography, which yields 3D views of a cell's architecture at molecular resolution. In addition, this technique was used to characterise in depth the path the virus takes within cells, and understand its mode of entry and the mechanisms underlying its release into the cell milieu. These are important data, because blocking the adhesion or the entry of the virus within cells is another of the potential therapeutic routes – for instance with drugs inhibiting the function of the spike protein or its receptor.

The non-structural proteins of viruses that participate in the "capping" of viral RNA/DNA to its functional form, as well as the host-cell enzymes that perform key steps in the synthesis of the nucleotides required for viral replication, are also of great relevance for therapeutic defence strategies, such as antiviral drugs. Here again, the complementary use of X-ray/neutron crystallography and cryo-electron microscopy, uniquely available at the ARIEs, will prove vital in providing the necessary high-resolution structural information.

In infected patients, viral antigens trigger the generation of antibodies, which can mark the virus for destruction by the immune system. Some of these antibodies can directly interfere with the life cycle of the virus, usually by binding to proteins involved in cell entry or replication. These antibodies are highly relevant for the development of a vaccine or an antibody-based therapy.

Identifying these antibodies, therefore, is yet another major therapeutic route. Several antibodies neutralising SARS-CoV-2 have been identified in the blood serum of infected patients in recent months. X-ray crystallography and cryo-electron microscopy could then be used to determine their 3D structure when bound to the viral proteins, in order to identify, in high resolution, the structural motif the antibodies recognise. This information is of utmost importance to understand the action of the antibody and whether it represents a promising target for further therapeutic investigation. It may also reveal those parts of the virus which are crucial for its infection, and which could be targeted via conventional drug development.

Finally, a campaign of measures to address the efficacy of antiviral drugs such as chloroquine, whose efficacy against COVID-19 is much discussed and controversial, is currently being carried out by an international team of experts at the FERMI free-electron laser, supported by complementary experiments at the Elettra synchrotron. A recent paper has also proposed the application of high-energy heavy-ion beams to inactivate SARS-CoV-2 virus particles with small damage to their spike proteins, to provide an intact virion for vaccine development (https://www.frontiersin.org/articles/10.3389/fphy.2020.565861/abstract).

Several examples of these above-mentioned key achievements are detailed in APPENDIX A.

4. OUTLOOK

The upcoming HE programme makes it possible to foster unique new initiatives at a European level. The ARIEs host the most sophisticated analytical technologies in Europe for analysing the pathology of viral and microbial infection at all length scales. X-ray/neutron crystallography, single-particle electron-microscopy and advanced laser technologies are optimally suited for guiding drug development, antiviral discovery and vaccine optimisation. Moreover, lasers are excellent tools for remote and in-field sensing in various environments. The increased coherence of X-ray beams available at current and future fourth-generation synchrotron sources will revolutionise X-ray imaging and fluorescence-microscopy techniques, allowing us to see the effects of a SARS-CoV-2 infection from a tissue to a molecular level. Moreover, the increased brilliance of the X-ray beams will massively boost the throughput of structure-based drug-design programmes, as well as the determination of the molecular structures and other characteristics of lead compounds and other potential antiviral drug candidates. Neutron scattering techniques offer unique and complementary insights into the underlying molecular mechanisms of infection, detection, treatment and prevention under physiological conditions, and are, thanks to deuterium-isotope labelling, particularly strong probes of the complex molecular assemblies that permit virus entry into host cells. Ion-irradiation facilities will also contribute to the detection and prevention of viral threats. High energy heavy-ion beams can provide inactivated viruses such as SARS-CoV-2 for vaccine development. Ion-track nanotechnology creates single-pore membranes for the development of rapid and highly sensitive virus sensors. Etched ion-track membranes with multiple pores and carefully designed geometries can form the basis of effective viral filtration solutions to help prevent outbreaks during pandemic situations. Complementary use of X-ray/neutron crystallography, X-ray/neutron scattering techniques and cryo-electron microscopy/tomography provide the structural details of processes at the molecular and atomic levels needed to understand the interaction of the virus with host cells – details that could lead to the identification of new therapeutic targets.

The ARIEs aim to make these large-scale research and operational efforts sustainable, learning from the experience gained during the COVID-19 crisis, to address current and future pandemics. They will continue to exploit and develop all these new ideas and technologies to offer effective solutions to the challenges posed by viral threats. For this, adequate funding schemes are necessary to (i) enable the facilities to continue to develop their preparedness for pandemics and remote operation, and (ii) establish and intensify networking activities and support for research within the health sciences.

5. CONCLUSIONS

The ARIEs represent the widest and most mature set of research infrastructures in the world. Supporting a growing community of some 40,000 researchers across Europe, and indeed the globe, they bridge scientific disciplines, academia and industry, and function as multi-faceted science and technology enablers. They have already demonstrated that they are able to stand together to confront societal challenges such as cancer and COVID-19. Their unique capabilities, skills and cultures – often reflected in their position on the ESFRI Roadmap – are critical to the analytics and characterisation of Viral and Microbial threats.

Despite the large contributions of the ARIEs to understanding the molecular basis of infections induced by SARS-CoV-2, we still have to find ways of mitigating the huge economic impact of COVID-19 and other pandemics. One possibility is the real-time screening of people and buildings. A fast, reliable, sensitive, low-cost and non-intrusive measurement for pathogens would allow large numbers of people to be tested when they go to work, dine at restaurants, attend events, and so on. While existing polymerase chain reaction (PCR) tests are fairly reliable, they are still too intrusive for routine screening, and there will always be a delay of at least several hours between taking a sample and obtaining its results. Costs, too, are still prohibitive for real mass screenings. To mitigate the economic impact of any major microbial health challenge in the future, new screening technology would probably need to employ light or magnetic fields for detection in real time; moreover, it would need to be scalable and applicable to other pathogens. With their outstanding record of technology development, we believe that the ARIEs are in an ideal situation to lead or support the development of such technology, in collaboration with the biomedical community.

This paper has given a taste of the wide-ranging capabilities available at the ARIEs, and the kind of advanced experiments and measurements that they can perform, to fight crises such as COVID-19. It has also described the kind of measures necessary to prepare for future microbial challenges. More capabilities will arise, especially as new generations of the ARIE facilities are constructed or upgraded. The ARIE Viral Threat approach will promote the integration of the Research Infrastructure ecosystem, and develop joint services that target complex research questions in crisis situations.

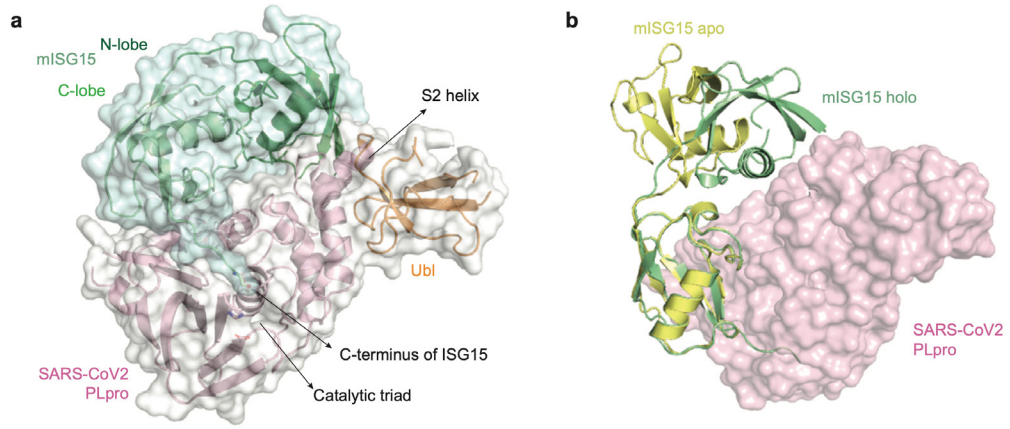
APPENDIX A

SOME EXAMPLES OF ARIEs KEY ACHIEVEMENTS

The crystal structure of the SARS-CoV-2 papain-like protease in complex with a non-covalent inhibitor

An example of active, on-going research for the development of anti-SARS-CoV-2 therapeutics relates to viral proteases. In the host cell the proteins essential to the life cycle of SARS-CoV2, as well as of many other viral pathogens, are expressed as a polyprotein, which has to be processed by viral and host proteases to produce the individual viral proteins. If the cleavage is inhibited by, for example, an anti-retroviral drug, then the machinery of virus replication is blocked. For the treatment to be efficient this inhibition has to be robust – that is, the drug should bind to the protease strongly. In this way there is an increased likelihood that treatments will be effective in the long run, despite mutations of the enzyme. High-resolution structural information on the proteases will help in the design of drug molecules inhibiting them. Here, X-rays have already delivered, on both the main and "papain-like" proteases of SARS-CoV-2, and efforts are underway to obtain suitable crystals of the main protease for neutron crystallography, which will provide complementary details about its hydrogen atoms – critical players in the binding of proteases to drug molecules.

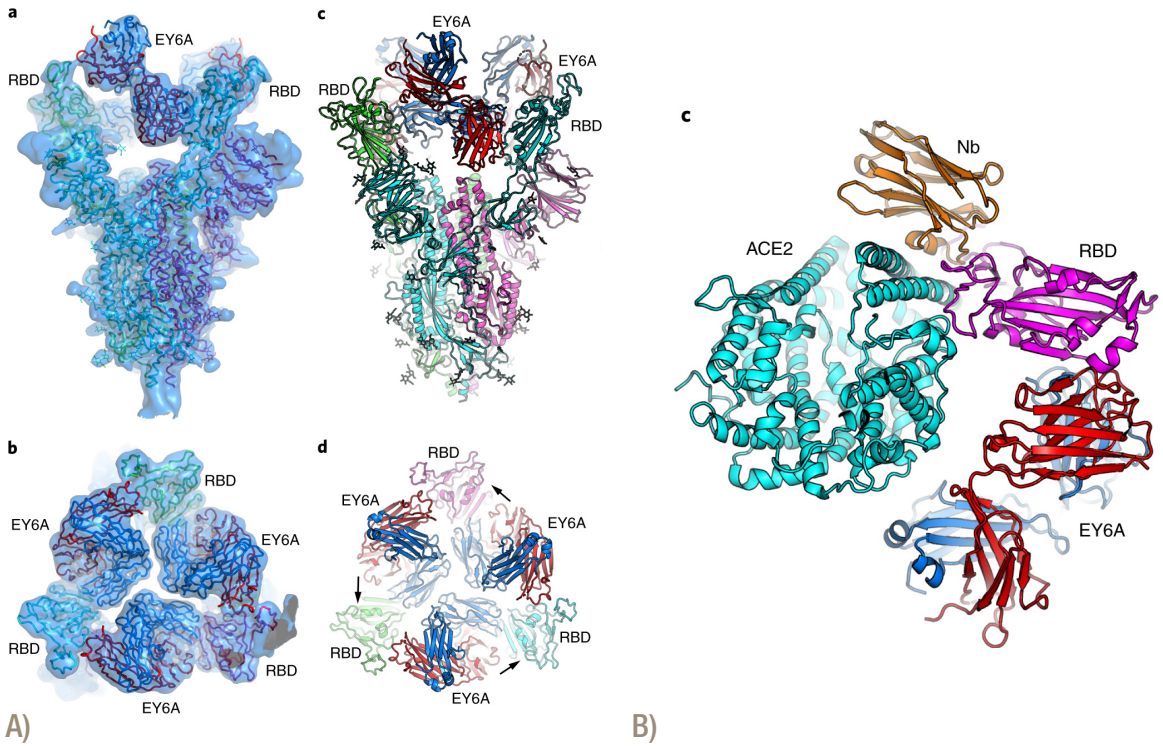
The X-ray work was led by scientists from the Goethe University in Frankfurt am Main, Germany, using the macromolecular crystallography beamline X06SA-PXI at the Swiss Light Source (SLS), following the synchrotron's „Priority COVID-19 call". As an example of the reactivity of the ARIEs to the COVID-19 pandemic, the SLS cancelled its planned Easter shutdown for this specific experiment's diffraction data to be collected. The papain-like protease is required for the processing of viral polypeptides and the assembly of new viral particles within human cells. In addition, SARS-CoV-2 uses the enzyme to dampen the host's anti-viral immune response for its own benefit, so that it can easily multiply and spread further. The researchers demonstrated that pharmaceutical targeting of the papain-like protease by a non-covalent inhibitor (GRL-0617) blocks the virus' spread and increases anti-viral immunity in human epithelial cells, the prime site of pathogen entry.



The three-dimensional structure of the SARS-CoV-2 papain-like protease (pink) in complex with the non-covalent inhibitor GRL-0617 (green) (Shin et al. 2020)

Details of neutralising antibody binding to the SARS-CoV-2 spike protein

Antibodies that can block the binding of the SARS-Cov-2 virus to the human receptor ACE2 have been used to treat critically ill patients, for example via blood-plasma transfusion from COVID-19 survivors. There is also evidence that antibody therapy can prevent serious symptoms from developing when administered before an individual is infected. A new study by a group at a hospital in Taiwan using the Electron Bio Imaging Centre (eBIC) at the Diamond Light Source synchrotron facility in the UK identified new antibodies called EY6A from a convalescent patient that could create a real potential for a new drug target, because they bind tightly to the receptor-binding domain (RBD) of the viral spike glycoprotein. In synergy with ACE2 blocking antibodies, these new antibodies could neutralize SARS-CoV-2 more strongly.

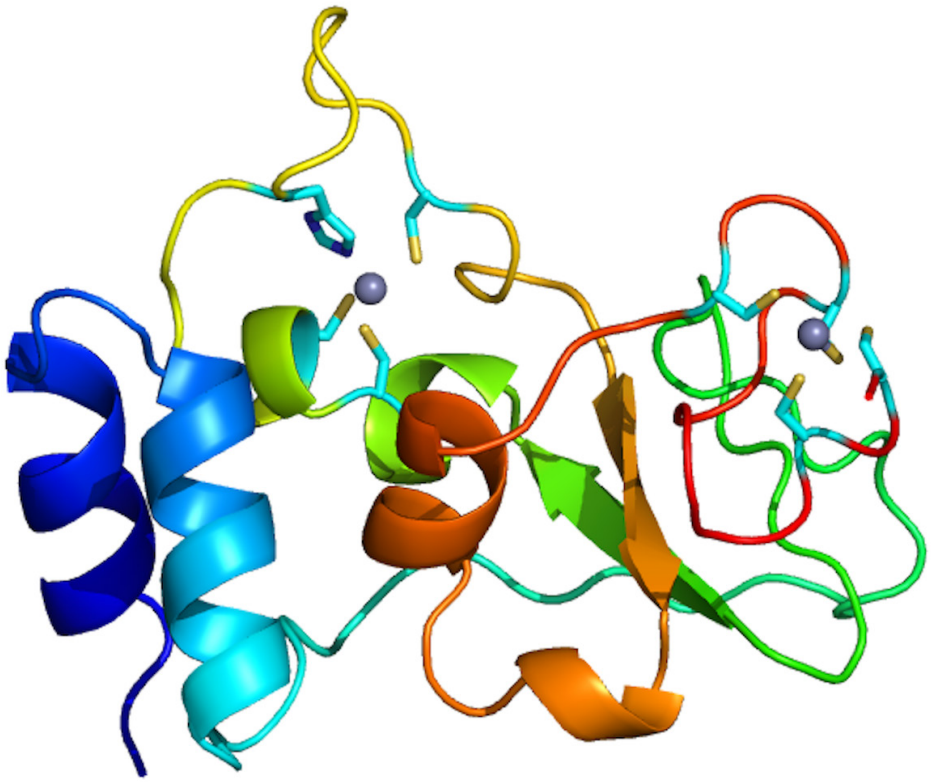


A) EM structure of the SARS-CoV-2 spike–EY6A Fab complex: side (a) and top (b) views showing three EY6A Fabs bound to the spike. B) A ribbon diagram of the 2.6Å X-ray crystal structure of the RBD (magenta) – EY6A (red/blue) – Nb (orange) ternary complex, with ACE2 (cyan) modelled in (cyan). (Zhou et al. 2020)

Structure of the non-structural protein Nsp10 involved in viral RNA capping during SARS-CoV-2 replication

To find an efficient drug that prevents SARS-CoV-2 from causing COVID-19, one important goal is to understand how to block the virus from replicating its genomic material. There are several proteins involved in the stages of RNA replication, viral-RNA proofreading and the protection of viral RNA by RNA-capping. An international collaboration

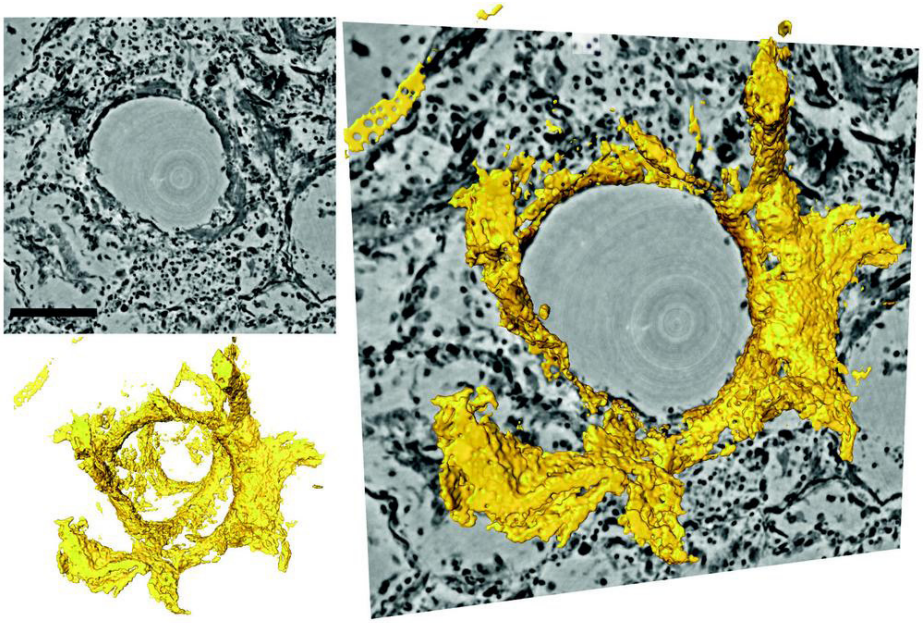
between the UK's UCL School of Pharmacy, Lund University's Lund Protein Production Platform and the ESS's Deuteration and Macromolecular Crystallisation (DEMAX) Laboratory has initiated biophysical and structural studies of three non-structural proteins of SARS-CoV-2, and recently succeeded in producing crystals of one of these proteins, Nsp10. The data was collected remotely via rapid access to the BioMAX beamline at the MAX IV synchrotron in Lund to approximately 2.6 Å resolution. A key part of the work is to establish the crystallisation conditions that will enable high-throughput, fragment-based screening for small, novel molecular inhibitors that block the viral replication cycle.



Ribbon representation of the first 2.6 Å X-ray crystal structure of a non-structural protein, Nsp10, which participates in viral-RNA capping during SARS-CoV-2 replication, as determined at the MAX IV synchrotron.

ARIEs provide new insights into COVID-19 lung tissue

In addition to the structural insights that will ultimately lead to the development of anti-SARS-CoV-2 therapeutics, the techniques available at the ARIEs are contributing to an understanding of the physiopathology of the virus. Here, researchers at the University of Göttingen, together with pathologists and lung specialists at the Medical University of Hannover, have developed a three-dimensional imaging technique that provides a high-resolution and three-dimensional representation of lung tissue damaged following severe cases of COVID-19. Using a special X-ray microscopy technique at DESY's high-brilliance X-ray source PETRA III, the researchers were able to image changes caused by the coronavirus in the structure of the alveoli (the tiny air sacs in the lung) and the vasculature. The results of the study have been published in the open-access journal eLife.



Sections through the three-dimensional reconstruction volume (upper left, grey) around a pulmonary alveolus surrounded by a “hyaline membrane” of dead cells (lower left, yellow). On the right, the images are superimposed. In the centre is the air bubble (alveolus). The electron density is represented by different shades of grey. The hyaline membrane, which the new method can represent as a three-dimensional structure for the first time, reduces gas exchange in the lungs and leads to respiratory distress. Credit: University of Göttingen, (M. Eckermann/T. Salditt 2020)

Meanwhile, the exceptional coherence provided by the newly upgraded ESRF-EBS synchrotron in Grenoble has allowed X-ray phase-propagation techniques to image large tissue samples, – in particular whole human organs, such as COVID-19-afflicted lungs – at near-micron resolution. This unprecedented capability means that scientists will be able to image, in a single experiment, the entire tower of a disease’s ramifications, from the anatomical down to the cellular level (manuscripts in preparation).

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Coimbra Laser Lab - CLL	www.uc.pt/en/uid/laserlab	Portugal
Centro de Laseres Pulsados - CLPU	www.clpu.es	Spain
Center for Ultrafast Lasers at UCM	www.ucm.es/ulc	Spain
Centre for Ultrafast Science and Biomedical Optics - CUSBO	www.fisi.polimi.it/en/research/european_facility/cusbo	Italy
National Agency for New Technologies, Energy and Sustainable Economic Development – ENEA-ABC	efrosf.frascati.enea.it/ife/abc.html	Italy
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