Coronavirus-related research and services at EMBL

Key visual for the virtual EMBL Conference 'SARS-CoV-2: Towards a New Era in Infection Research'. Credit: Aleksandra Krolik/EMBL

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European Molecular Biology Laboratory
Laboratoire Européen de Biologie Moléculaire
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Introduction

1. The molecular life sciences have a central role in delivering new treatments or vaccines against SARS-CoV-2. EMBL has re-purposed existing facilities to provide a range of direct research and support services, including in partnership with institutes in Member States.

2. This document provides a summary of EMBL coronavirus-related research and service activity as of 10 November 2020, and will be updated as additional projects receive necessary safety and scientific approvals.

Update highlights

3. The High-Throughput Crystallisation (HTX) Lab at EMBL Grenoble provides access to a fully automated protein-to-structure pipeline to support COVID-19-related projects by internal and external users. Two projects are currently underway (see item 18).

4. The Sample Preparation and Characterisation (SPC) Facility at EMBL Hamburg is open to support scientists working on COVID-19 research. As one of the best equipped facilities in Europe, the SPC facility is in high demand from external users and has been involved in several COVID-19-related projects with national and international collaborators (see item 19).

5. EMBL scientists have established a robust protocol for the detection of coronavirus using next-generation sequencing, called 'Multiplexed COVID-19 Quantification' (McQ), which can process more than 5 000 samples in parallel. An experimental weekly testing campaign has been implemented at EMBL Heidelberg to test the applicability of McQ for regular population-scale testing and compare its performance with other technologies (see item 22).

6. An international team of researchers, including EMBL-EBI scientists, are exploring how existing drugs can be repurposed to prevent SARS-CoV-2 from rewiring human proteins. They identified over 70 drugs that may be repurposed to treat COVID-19 patients. Clinical trials for six compounds have been launched or are in planning (see item 25).

7. Scientists at EMBL Hamburg and their collaborators have identified and structurally analysed synthetic antibodies – known as nanobodies – that bind to the SARS-CoV-2 spike protein and prevent viruses from infecting cells *in vitro* (neutralisation). In the future, nanobodies have the potential to be

used as compounds to stop SARS-CoV-2 from infecting humans, or as tools in coronavirus diagnostic tests (see item 27).

8. A team of electron microscopy experts from EMBL's Electron Microscopy Core Facility and Schwab team performed a full study of SARS-CoV-2-infected human lung cells, which were shared by colleagues at Heidelberg University Hospital, to better understand the changes in cell structures occurring in infected cells. The analysis revealed the role of cellular organelles in virus replication and virion formation and will be a stepping stone to support the development of new treatments against COVID-19 (see item 29).

9. Scientists at EMBL, the German Cancer Research Center (DKFZ) and Heidelberg University Hospital are studying how the novel coronavirus behaves in the gut. They identified a subpopulation of intestinal cells as the prime target of SARS-CoV-2. Strong pro-inflammatory programmes in these cells may contribute to systemic inflammation observed in COVID-19 patients (see item 30).

10. Several COVID-19-related research projects have been summarised in preprints or published as open-access publications (see items 23, 25, 27, 30, 31).

TOP

Calls to action

11. EMBL is asking its Member States for contacts to COVID-19 serology studies. As part of the European COVID-19 Data Platform, EMBL-EBI has the means to store and share this type of data through the BioStudies database, and is interested in working with the community of serology data producers and users on minimal reporting standards to sort out privacy issues and maximise interoperability.

12. EMBL-EBI scientists are following with interest wastewater testing as a means to track the spread of coronavirus and consider establishing a data sharing group for this purpose. We encourage feedback from Member States on the extent of ongoing testing activities, to explore whether the development of shared reporting standards, data storage and data sharing infrastructures in a European context will be beneficial.

TOP

Services for Member States

13. Rapid data access, analysis and visualisation
    EMBL's European Bioinformatics Institute (EMBL-EBI) launched the COVID-19 Data Platform in conjunction with the European Commission, the European Open Science Cloud, ELIXIR and a number of partner institutions across Europe. The aim is to enable rapid access to datasets and results pertaining to the SARS-CoV-2 pandemic, which will accelerate research and support the development of diagnostics, therapeutics and effective vaccines.

The Platform consists of three connected components:

- Data Hubs which organise the collection of sequence data from the outbreak and provide open data sharing for the European and global research communities
- Federated European Genome-phenome Archive (EGA) which supports controlled access sharing of human COVID-19 biomolecular and phenotypic data
- COVID-19 Data Portal, which brings together, and is continuously updated with relevant COVID-19 datasets and tools.

In the first six months of its existence, the COVID-19 Data Portal has recorded above three million web requests by around 99 000 users from more than 175 geographical locations, including most of the European countries. Over 300 institutions from 40 countries have deposited data and the Portal currently offers open access to over 100 000 SARS-CoV-2 sequences, over 1 000 host sequences and 180 000 publication records.

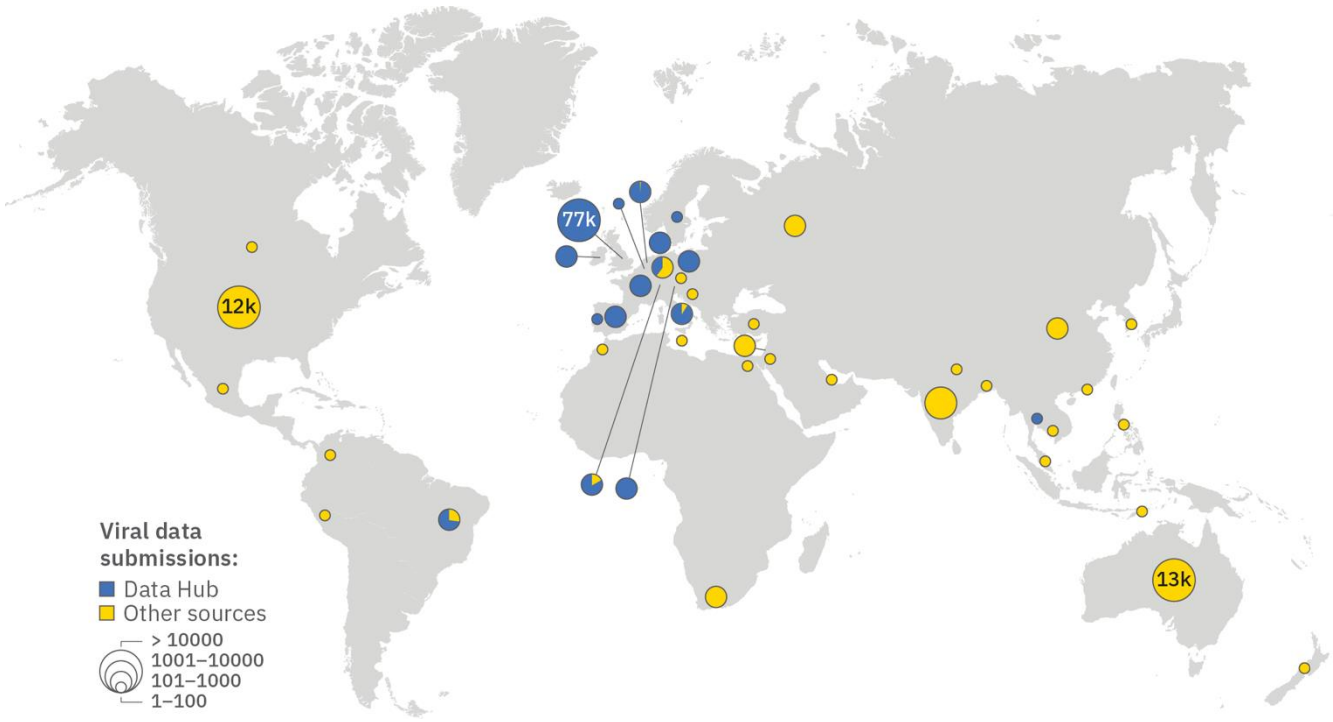

Figure 1: *World map of raw viral data submissions. 'Other sources' include sequences submitted via the International Nucleotide Sequence Database Collaboration (see main text). Date: 3 November 2020.*

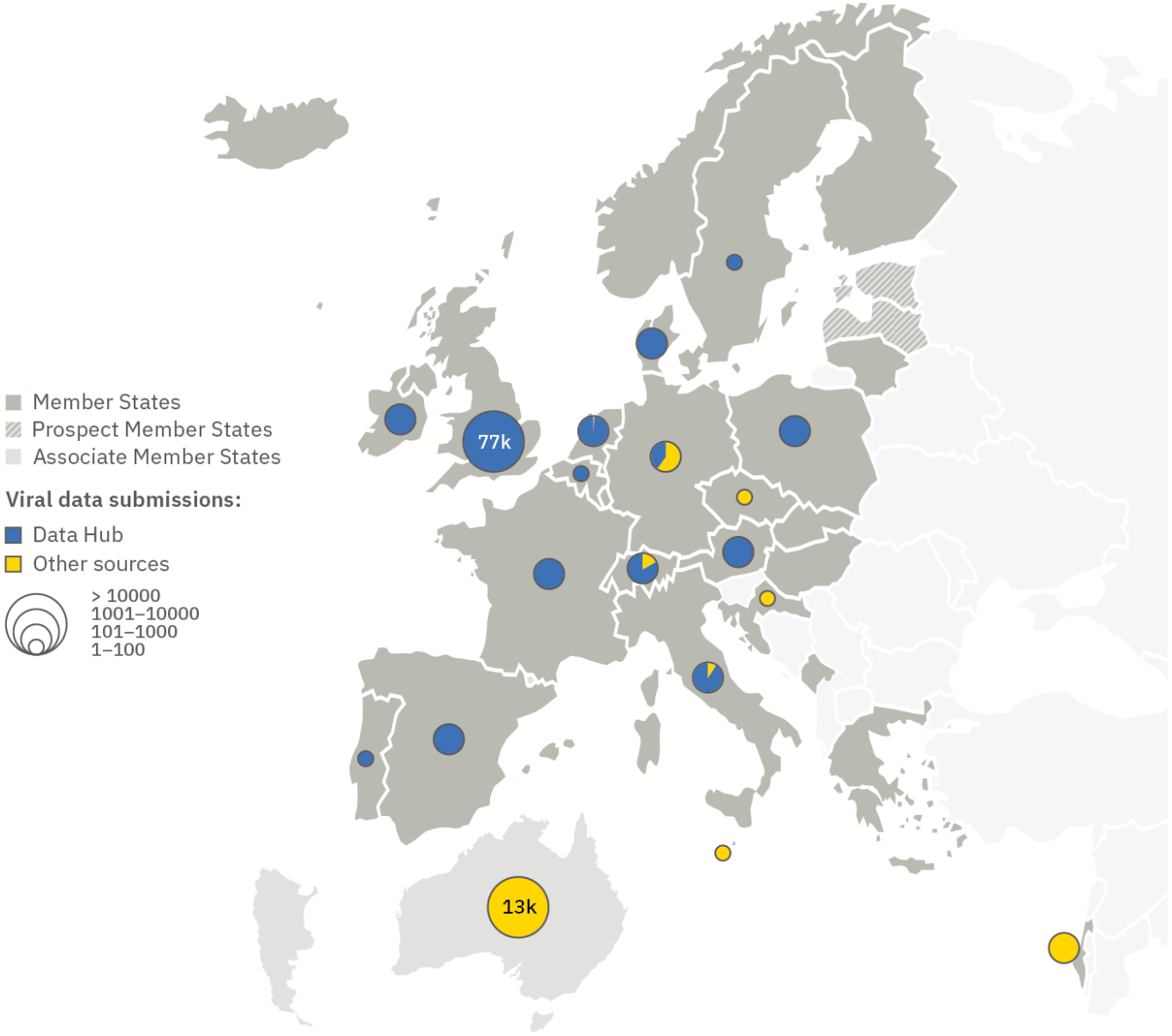

Figure 2: *Contributions of raw viral sequence data from Member States. 'Other sources' include sequences submitted via the International Nucleotide Sequence Database Collaboration (see main text). Date: 3 November 2020.*

The functionality of the Data Portal is steadily improving. Users can now access the latest microscopy data and a drug target prioritisation tool developed by Open Targets. We are looking to extend specifically into serology data and potential wastewater tracking.

The Data Portal also provides an off-the-shelf model that any country can use and build on, in order to bundle national research efforts and to offer guidelines, tools and services to support its researchers. Norway, Poland, Slovenia, Sweden and Japan have already launched their own National Data Portals,

each showcasing different functionalities and data, according to national requirements. These countries continue to also feed their data through the COVID-19 Data Platform.

In addition, the Platform as a whole enables the coordination of viral genome sequence data across Europe, and globally via International Nucleotide Sequence Database Collaboration. A specific feature offered to our Member States is the provision of support for setting up Data Hubs where viral genome sequence data can be coordinated (e.g., from a particular nation) with controlled public release. So far, we have engagement on Data Hubs from 18 Member States, Associate Member States, and Prospect Member States.

Many EMBL-EBI data resources, such as the Protein Data Bank in Europe (PDBe), UniProt, the Electron Microscopy Data Bank, RNAcentral, ChEMBL, PRIDE and Ensembl, have released dedicated datasets and tools for SARS-CoV-2 research.

Data from these specialised platforms are accessible directly through the COVID-19 Data Portal and allow for more in-depth analysis of specific data types.

EMBL-EBI's Europe PubMed Central (Europe PMC) open science platform has begun to index COVID-19 preprints and includes information on COVID-19-related funding grants to make the information more widely available and accessible.

14. Epidemiological situational awareness
EMBL-EBI can also provide connections to leading infectious epidemiology groups for situational awareness of the outbreak to enable open and scalable infectious epidemiology analysis that can be fed by national and regional information. Additional national-level secure data feeds may also be available should EMBL Member States wish to pursue this option.

EMBL has joined the Versatile Emerging Infectious Disease Observatory (VEO) consortium, an EC-funded international collaboration of 20 research institutions and universities to investigate outbreak scenarios and develop new methods to classify the risk and impact of future outbreaks.

15. Human genetic information
EMBL-EBI is coordinating human (host) genetic information on the infection and response to COVID-19, via the Europe-wide federation of the European Genome Phenome Archive (EGA), which is a joint project from EMBL-EBI and the Centre for Genomic Regulation (CRG).

Globally, the EGA is supporting the COVID-19 Host Genetics Initiative to form the host data sharing platform in collaboration with the NIH AnVIL platform. The COVID-19 host genetics initiative brings together the human genetics community to generate, share, and analyse data to learn the genetic determinants of COVID-19 susceptibility, severity, and outcomes. Such discoveries could help to generate hypotheses for drug repurposing, identify individuals at unusually high or low risk, and contribute to global knowledge of the biology of SARS-CoV-2 infection and disease.

To date the EGA has processed three submissions totalling 2.75 terabytes of data, which are now fully available for access requests and part of the COVID-19 Data Portal. The Helpdesk team continues to provide expedited support to a handful of ongoing submissions and we expect these submissions to continue to increase in the coming weeks.

16. Deciphering the genomics behind COVID-19
    EMBL is providing expertise in establishing IT infrastructures to support the collection, distribution, and analysis of genomic data from COVID-19 patients, as part of the German COVID-19 OMICS Initiative (DeCOI) involving more than 20 universities and research institutes.

    DeCOI brings together experts in genomics, bioinformatics, and national data infrastructure initiatives. EMBL scientists lead a task force in the context of the European Bioinformatics Infrastructure ELIXIR to funnel such data into the German Human Genome–Phenome Archive (GHGA), and further to the European COVID-19 Data Platform for rapid world-wide sharing.

    Combining the data that will be generated in large clinical studies across Germany and Europe will be necessary to determine the influence of our genes on coronavirus infections and infection severity.

17. Comorbidity risk assessment
    EMBL-EBI can provide Member States with the TensorCox software and necessary operational expertise to perform COVID-19 comorbidity risk assessments, potentially using all health records from across a country (if accessible). The software has been successfully run on datasets of six million individuals and is expected to be able to scale to 100 million people.

    The software would need to be run in a secure data environment nominated by the EMBL member state, for example in a national facility.

18. Re-opening Structural Biology services at EMBL Grenoble
    EMBL has re-opened the High-Throughput Crystallisation (HTX) Lab at Grenoble to provide access to a fully automated protein-to-structure pipeline. Researchers are able to send their samples to the facility and to access their results from their desktop, using the Crystallographic Information Management System (CRIMS).

    CRIMS is able to communicate with the European Synchrotron Radiation Facility (ESRF) synchrotron in Grenoble and the PETRA III synchrotron in Hamburg, to support automated and remote X-ray data collection.

    The HTX Lab is currently supporting two COVID-19-related projects. An external collaborator is applying the automated CrystalDirect technology to advance their project. In an EMBL-internal collaboration, scientists have initiated a fragment screening project (see item 34).

    Together with ESRF, EMBL has restarted the activities of the Joint Structural Biology Group in Grenoble to support coronavirus-related projects. A new initiative will allow users to be granted access to the HTX lab at EMBL and to a macromolecular crystallography (MX) beamline at the ESRF with a single project proposal. The initiative will enable a streamlined process through crystal production, testing, and data collection. The high automation of HTX and the MASSIF beamline are unique and will be very valuable to support structural biology projects in conditions of confinement. Since the JSBG beamlines, notably MASSIF-1 and ID23-2, came back for user operation, they have processed over 200 crystals of SARS-CoV-2 protein targets for drug discovery.

19. Re-opening Structural Biology services at EMBL Hamburg
At EMBL Hamburg, the Sample Preparation and Characterisation (SPC) Facility has reopened to support scientists working on COVID-19 research. The SPC Facility is one of the best equipped facilities in Europe and is therefore in high demand from external users for COVID-19 projects.

In collaboration with DESY, Hamburg University, and the Heinrich-Pette-Institut (HPI), the SPC Facility has performed biophysical characterisation and optimisation experiments on two SARS-CoV-2 proteases (MPro and PLPro) and two non-structural proteins (nsp7+8) to support structural studies.

Colleagues at DESY identified two compounds in an X-ray based screen of drugs against SARS-CoV-2 main protease (MPro), and the SPC facility performed biophysical characterisation of the interaction of these compounds with the viral protease (manuscript in preparation).

In collaboration with colleagues at DESY and in Leipzig, Vienna, and Singapore, the SPC facility measured interactions of the SARS-CoV-2 E-protein with lipid membranes. Another collaborative project with colleagues at EMBL Hamburg and in Argentina investigated hotspots for biochemical modification on the spike protein's receptor binding domain (manuscript in preparation).

The SPC facility was also involved in the identification of synthetic antibodies against SARS-CoV-2 (see item 27).

Data on MPro protein crystals, obtained by collaborators at DESY, have been collected at the DESY and EMBL X-ray crystallography beamlines. Both EMBL Hamburg beamlines are also operating for remote user access.

Also at EMBL Hamburg, the small-angle X-ray scattering (SAXS) P12 beamline has resumed its activity as a Structural Biology service and implemented fast-track approval for COVID-19-related projects. So far, seven internal and external projects were conducted (see item 33).

20. Re-opening the cryo-EM service platform at EMBL Heidelberg
To help the scientific community advance essential coronavirus research projects, EMBL reopened its cryo-EM service platform at EMBL Heidelberg during the shutdown of the Heidelberg site from mid-March to beginning of May 2020.

EMBL experts carried out data collection in close consultation with users and performed cryo-electron tomography studies on viral particles that led to a manuscript recently published in Science (see item 31). Since partial reopening of EMBL Heidelberg in May 2020, service is no longer restricted to corona virus research and all users can send their samples to the cryo-EM service platform.

21. Producing proteins for coronavirus research
Testing samples for coronavirus requires enzymes – proteins that perform a specialised task. The Protein Expression and Purification Core Facility (PEPCF) at EMBL Heidelberg is producing these enzymes using bacteria as host organisms. The enzymes are now being used in the 'Multiplexed COVID-19 Quantification' assay developed by colleagues at EMBL Heidelberg (see item 22), and the newly developed workflows are currently being summarised in a joint manuscript.

PEPCF is also providing enzymes for a coronavirus testing assay developed by colleagues at the Zentrum für Molekulare Biologie der Universität Heidelberg (ZMBH), and the protocols and expression constructs are being shared with other academic groups as well.

PEPCF has successfully produced the SARS-CoV-2 spike protein and its receptor-binding domain, the human ACE2 receptor, the viral Nsp5 protease and Nsp12 catalytic subunit of the viral polymerase, providing these proteins to several other coronavirus-related research projects at EMBL, to assist the development of new strategies to fight the virus.

TOP

Research

22. New methods to scale up coronavirus testing
A team of EMBL Heidelberg scientists has established a robust protocol for the detection of coronavirus using next-generation sequencing, called 'Multiplexed COVID-19 Quantification' (McQ), which can process more than 5 000 samples in parallel. The assay has been automated and optimised to use almost exclusively enzymes produced by PEPCF (see item 21) and non-proprietary buffers to avoid reagent shortage.

The scientists have benchmarked McQ using over 800 patient samples, demonstrating its sensitivity and accuracy. An experimental weekly testing campaign has been implemented at EMBL Heidelberg to test the applicability of McQ for regular population-scale testing and compare its performance with other technologies. A manuscript describing the McQ protocol is in preparation. In future, McQ could help scientists and clinicians to regularly test large parts of the population.

23. Developing an imaging-based antibody screening method to perform clinical immunity studies
Scientists at EMBL Heidelberg have been involved in the development of a microscopy-based assay for the semi-quantitative detection of SARS-CoV-2 specific antibodies in human sera. By providing high-throughput image processing technology, the scientists enabled the semi-automated detection of antibodies against the entire viral proteome.

The approach is summarised in a preprint and has been applied in a study on the 'Prevalence of SARS-CoV-2 infection in children and their parents in southwest Germany', which analysed the co-occurrence of SARS-CoV-2 infections in children and their parents and was jointly conducted by the University Hospitals in Heidelberg, Tübingen, Ulm, and Freiburg. All raw images and processed data have been made freely available via EMBL-EBI's BioImage Archive.

24. Identifying how potential COVID-19 drugs work
EMBL researchers are using a technology called thermal proteome profiling (TPP), which can systematically identify targets for drugs in living cells. A number of drugs that have been reported to potentially help against COVID-19 have been analysed by TPP to better understand their mode of action. The data is currently being analysed and follow-up experiments are being discussed. The study may help scientists to quickly propose efficient drugs or drug combinations to treat COVID-19, which are urgently needed until a vaccine is developed and made available globally. The project relies on

methods developed in the Genome Biology Unit and services provided by EMBL's Proteomics Core Facility.

25. Repurposing existing drugs to prevent SARS-CoV-2 from rewiring human proteins
An international team of researchers has analysed how SARS-CoV-2 hijacks the proteins in its target cells. One study, in which EMBL-EBI scientists took a leading role, was published in *Cell*. It shows how the virus shifts the cell's activity to promote its own replication and to infect nearby cells. The scientists also identified seven clinically approved drugs that could disrupt these mechanisms.

    Clinical trials for six compounds have been launched or are in planning to assess their potency and safety in treating COVID-19 patients. The study has received wide attention in the media, including articles from the *San Francisco Chronicle*, *BBC Mundo*, and *The Financial Times*.

    In another study, published in *Nature*, the scientists investigated the interactions between viral and human proteins. They identified 66 SARS-CoV-2-interacting human proteins for which 69 drugs already exist or are under development. These drugs may be repurposed to treat COVID-19 patients as well.

    In the third study, published recently in *Science*, the team of almost 200 researchers from 14 leading institutions in six countries compared how SARS-CoV-1, SARS-CoV-2, and MERS differ in using human proteins for their replication. They identified common drug targets and the drugs that act on them. These drugs could be repurposed as COVID-19 treatments and could help us to respond more rapidly to emerging coronavirus strains in the future.

    EMBL-EBI scientists continue to be heavily involved in follow-up work to these three studies.

26. Detecting SARS-CoV-2 antibodies
EMBL researchers are developing a test that can diagnose whether someone has been infected by SARS-CoV-2 in the past. The test is not intended as a clinical diagnostic but instead to support scientific and epidemiological studies.

27. Exploring synthetic antibodies to stop coronavirus
Scientists working at EMBL Hamburg and their collaborators at Karolinska Institutet Stockholm have identified and structurally analysed synthetic antibodies – known as nanobodies – that bind to the spike surface protein of the novel SARS-CoV-2 coronavirus and prevent viruses from infecting cells *in vitro* (neutralisation). The scientists further improved the binding strength of the selected nanobodies by generating derivatives, increasing their neutralisation efficiency more than 300-fold.

    The results have been made available in a preprint and published in *Nature Communications*. Selected nanobodies are now available in different formats for the community and protein samples have been sent to collaborators to explore further applications. In the future, nanobodies have the potential to be used as compounds to stop SARS-CoV-2 from infecting humans, or as tools in coronavirus diagnostic tests. The study has been covered in over 100 online media outlets from around the world, including *Science Daily (US)*, *ABC Online (Spain)*, *India TV* and *MSN (Netherlands)*.

28. Identifying neutralising antibodies against SARS-CoV-2
    EMBL scientists will use droplet microfluidics techniques to screen blood serum from recovered COVID-19 patients for neutralising antibodies that could potentially stop the infection before it enters the cell.

    Collaborators at the University of Bergen will carry out validation experiments on the nature of the antibodies detected. The work could eventually contribute to targeted treatments for COVID-19 and also enable the identification of related neutralising antigens that could support vaccine development.

29. Taking a closer look at infected cells to better understand COVID-19
    Little is known about the mechanisms used by coronavirus to infect and destroy its target cells in humans. To better understand the changes in cell structures occurring in cells infected by SARS-CoV-2, the Department of Infectious Diseases at Heidelberg University Hospital shared samples of infected human lung cells with a team of EMBL electron microscopy (EM) experts.

    EMBL scientists performed a full study of infected cells, including transmission electron microscopy, electron tomography, and focused ion beam scanning electron microscopy (FIB-SEM) of cells at different time points post-infection. The analysis revealed the role of cellular organelles in virus replication and virion formation and identified structures in cells that undergo changes after infection with the virus. The results of this collaborative work have been accepted for publication in *Cell Host & Microbe* and will be a stepping stone to support the development of new treatments against COVID-19.

30. Understanding how SARS-CoV-2 behaves in the gut
    Scientists at EMBL, the German Cancer Research Center (DKFZ), and Heidelberg University Hospital are studying how the novel coronavirus behaves in the gut. By combining advanced imaging and sequencing technologies to study coronavirus in human intestinal cells and organoids – lab-grown clusters of cells that develop features of our small intestines – the scientists found that intestinal epithelial cells fully support the SARS-CoV-2 replicative lifecycle.

    They also observed a strong, type III interferon-mediated immune response upon viral infection in these cells, which efficiently reduced virus replication and production. The work, which has been summarised in a preprint and published in *Cell Reports*, fills gaps in our understanding of SARS-CoV-2 epidemiology and identifies the gastro-intestinal tract as an active site of SARS-CoV-2 replication.

    In a follow up study, the scientists have performed single-cell RNA sequencing experiments on infected cells. They identified a subpopulation of intestinal cells as the prime target of SARS-CoV-2 in the gut. Infected cells activated strong pro-inflammatory programmes and interferon production, but the virus interfered with interferon-induced gene activation in these cells. Uninfected bystander cells showed strong responses, indicating that the gut contributes to systemic inflammation observed in COVID-19 patients. The results have been made available in a preprint.

31. Studying the structure of SARS-CoV-2 spike protein
    Scientists at EMBL Heidelberg, the Max Planck Institute of Biophysics, the Paul Ehrlich Institute, and Goethe University Frankfurt/Main have employed cryo-electron tomography and molecular dynamics

simulations to study the structure of SARS-CoV-2 spike protein on viral particles. They observed an unexpected level of flexibility within the spike, which may allow the protein to scan host cell surfaces.

They also found a protective coat of sugar molecules on the spike protein, which hides it from antibodies, which has important implications for the development of vaccines and therapeutics. The results were made available in a preprint and as a publicly available dataset, and have recently been published in *Science*. The study has been covered in over 70 online media outlets, including *Frankfurter Allgemeine Zeitung* (*FAZ.net,* Germany), *net.hr* (Hungary) and *La Patilla* (Venezuela).

32. Understanding the SARS-CoV-2 infection cycle
Changes in the thermal stability of proteins are linked to their functions. Using thermal proteome profiling (TPP, see item 24), EMBL scientists aim at better understanding the infection cycle of the novel coronavirus. They adapted the TPP technology to high biosafety conditions and performed time-course experiments to monitor how SARS-CoV-2 infection affects the thermal stability of the proteome. TPP uncovered additional candidate proteins that play a role in coronavirus infection and could potentially be targeted therapeutically. A manuscript is submitted and will be posted as a preprint very soon.

33. Using small-angle X-ray scattering to study the structure and interaction of SARS-CoV-2 molecules
Researchers at EMBL Hamburg are studying COVID-19-related molecules by exposing them to high-brilliance X-ray beams, using biological small-angle X-ray scattering (SAXS). SAXS makes it possible to reconstruct the 3D shapes of crucial molecular units in a cell or virus directly in near-native solutions.

The technique was used to elucidate the interactions of the viral receptor binding domain with synthetic antibodies (see item 27). In another project with colleagues in Boston (US) and Cambridge (UK), EMBL scientists investigate the structure of the viral spike glycoprotein S1 and the complex it forms with an antibody in solution. Data on open and closed forms of the spike was obtained and is presently being analysed. The research is part of a global effort by scientists to elucidate the structural organisation of SARS-CoV-2 proteins, identify key antibodies, and pinpoint molecular drug targets to hopefully halt the virus in its tracks.

34. Mechanistic insights into SARS-CoV-2 biology
Scientists at EMBL Grenoble are combining X-ray crystallography, cryo-electron microscopy, nuclear magnetic resonance, and small-angle X-ray scattering to try to solve some of the puzzles of the novel coronavirus's molecular mechanics. They are studying several viral key targets, such as the virus's replication machinery and the protein the virus uses as a pair of molecular scissors to set other viral proteins free.

A fragment screening project has been initiated with the HTX lab (see item 18) to identify small molecules targeting the SARS-CoV-2 protease PLP2pro. Samples have been produced and crystallisation screening is underway.

The second project aims at determining the mechanism of action of novel nucleoside analogue inhibitors of the SARS-CoV-2 replication machinery, in collaboration with a pharmaceutical company. Samples are currently being analysed by cryo-electron microscopy at EMBL Heidelberg.

In the third project, EMBL scientists are studying regions of the viral RNA genome that are not directly translated into proteins but can nevertheless form complex structures that contribute to the translation of genomic information into viral proteins.

These synergistic research efforts aim to dissect key mechanistic aspects of coronavirus molecular machines and potentially accelerate the development of new antivirals to contain the pandemic.

35. Editing the mouse genome to study SARS-CoV-2 infection
To study how SARS-CoV-2 infects cells, researchers can use mice that have had their genome modified so that they express a human version of a protein called ACE2 – the receptor that binds the SARS-CoV-2 spike protein and allows the virus to enter the cell. However, the transgenic mice currently available do not show the full disease spectrum observed in human patients.

The Gene Editing and Embryology Facility (GEEF) at EMBL Rome is generating a sophisticated transgenic mouse line that could help to solve this problem. Instead of adding artificial copies of human ACE2, the scientists subtly edit the mouse version of the gene so that the protein it produces is like the human version only at critical points where it interacts with the SARS-CoV-2 spike protein. Initial data indicate the successful editing of the ACE2 gene at the first critical site; once confirmed, the other critical points will be targeted.

36. Silencing the SARS-CoV-2 receptor with epigenetic modifications
Scientists at EMBL Rome have recently developed a new version of a CRISPR molecular tool used for epigenome editing, making it smaller and easier to deliver into cells. This tool is able to cause targeted epigenetic modifications of specific genes in specific cell populations.

The scientists currently optimise this tool in mice to target airway cells that express the ACE2 protein. Once directed to these specific cells, the editing system is able to cause epigenetic modifications that temporarily silence the expression of ACE2.

The expected outcome is to block the entry route for the virus and make cells resistant to SARS-CoV-2 infection. The project will investigate the wider potential of epigenetic editing as a general strategy for future prevention or treatment options. It has been featured on Technologynetworks.com in an interview with EMBL group leader Jamie Hackett.

37. Using data science to help our fight against SARS-CoV-2
EMBL has launched a diverse set of data science projects on COVID-19, including exploration of host genetics, drug repositioning for COVID-19 treatment, protein-protein interactions to better understand the operation of the virus, viral RNA biology, and single cell genomic analysis.

Many of the research projects mentioned above apply data science approaches. EMBL-EBI researchers have also been involved in recently published studies that explore computational strategies to combat COVID-19 and analyse the perils of ignoring metadata standards when reporting COVID-19-related data.

38. Helping researchers identify host proteins used by coronavirus
EMBL scientists have created the RBPbase database, which stores information on more than 4 000 proteins that have been identified as RNA-binding proteins (RBPs) across multiple studies. RNA viruses, such as SARS-CoV-2, require cellular RBPs as host factors to create more copies of themselves and influence cellular functions.

    RBPbase is regularly updated and forms the basis of a review that has recently been accepted for publication in *Nature Reviews in Genetics*. So far, the database has been accessed by over 850 unique users from 44 different countries and has been mentioned in five bioRxiv preprints. It will help researchers worldwide to identify candidate proteins in infected cells as coronavirus-interacting RBPs. This may lead to a better understanding of how SARS-CoV-2 multiplies in cells, and may enable the design of novel therapeutic strategies.

39. Distinguishing coronavirus genome mutations from inadvertent errors
Scientists at EMBL-EBI have performed a large-scale analysis of over 4 700 SARS-CoV-2 genomic sequences. They found that many of the apparently most interesting changes in the SARS-CoV-2 genome that have been reported so far are likely to be technical artefacts, rather than biological mutations.

    Based on their analysis, the EMBL scientists and their colleagues developed a set of recommendations for the analysis of SARS-CoV-2 genomic data. This will help other researchers to interpret SARS-CoV-2 genomic sequences and ensure the mutations they identify are real. The recommendations are updated regularly and are freely available via an online epidemiology forum.

40. Understanding the neurophysiological mechanisms underlying social aggression and avoidance
In a study recently published in *eLife*, scientists at EMBL Rome investigated defensive behaviour in mice, to better understand how our brains make 'fight or flight' decisions in conflicts over territory, mates, or food.

    The researchers studied neurons in a specific region of the mouse brain, which receives sensory inputs related to emotional behaviour and sends motor outputs to enact an adequate response. They observed activation of a large class of neurons that increased proportionally with the intensity of the threat, promoting the defensive response. The same neuronal activity was triggered in the absence of a threat when mice returned to another animal's territory in which they had experienced a threat before – demonstrating that these experiences are encoded in a socio-spatial context.

    The study received wide attention in the media, including from *Science Daily*, and the research was featured in an article from *National Geographic* on social fear in COVID-19 times. Finding yourself in a crowd or meeting strangers who don't comply with social norms, such as distancing measures or wearing masks, can lead to anxiety, aggression, or avoidance – but they are experienced at different levels of discomfort by individual persons. The results of this research may help us to better understand how humans react to social threats and disentangle the neuronal processes that underly an individual's decision to fight or flight.

TOP

Training and courses

Past activities

41. EMBL has transitioned many physical courses and conferences to virtual offerings, following the success of the initial virtual conference, the EMBO | EMBL Symposium: The Four-Dimensional Genome at the end of March. So far in 2020, 14 conferences / symposia and 11 courses have been offered online by the EMBL International Centre for Advanced Training (EICAT) with the Course and Conference Office (CCO) and EMBL-EBI Training, which attracted a total of 7 100 participants of over 110 nationalities residing in over 90 countries, including 483 virtual chairs and speakers. Upcoming virtual conferences and courses are listed under item 44.

    External Training has also launched a new online learning platform, 'EMBL eCampus', implemented a virtual social programme, and offer fee waivers and childcare grants for virtual events. A total of 494 fellowships and fee waivers were granted to virtual event participants so far. In addition, virtual event platforms have been tested in order to find the best format for EMBL-organised conferences.

42. EMBL hosted the Virtual EMBL Conference: SARS-CoV-2: Towards a New Era in Infection Research on 3 July, which brought together leading experts in virology, infectious disease pathogenesis, structural biology, molecular and cellular biology, immunology, drug discovery and resistance, vaccinology, data science, and epidemiology.

    The speakers presented latest findings from their research on SARS-CoV-2 and other viruses, showed first epidemiologic data on the ongoing pandemic, and addressed current limitations in our scientific understanding of emerging pathogens. They highlighted the importance of basic research, collaboration, and data sharing in containing the SARS-CoV-2 pandemic, and discussed opportunities to improve the response to pandemics in future. Many of the presentations have been made freely available online.

    EMBL also hosted the Virtual Conference: The impact of the COVID-19 crisis on women in science: Challenges and Solutions with over 1 300 registered participants on 9 September, to discuss the indirect impacts of the coronavirus pandemic on women in science. Presentations from this conference have been made available online as well.

    The EMBL Science & Society Programme has initiated a new seminar series 'Infectious Disease & Society'.

43. The European Learning Laboratory for the Life Sciences (ELLS) offers two new virtual programmes for science teachers and students. The virtual formats will increase our capacities to allow more students and teachers to take part in EMBL's educational activities.

    The aim of the EMBL Virtual School Visit programme is to make life sciences come alive in classrooms. Groups of secondary school and high school students are able to connect in real time with EMBL scientists, hear about their research, discover career options in the life sciences, and experience an interactive visit to EMBL's facilities and laboratories. The first virtual school visit by a school from Ukraine was hosted in October 2020. The second virtual school visit will be run with around 100 Greek students in mid-November, closing the programme's pilot phase. Offering virtual

visits free of charge, in a flexible format, and in different languages improves accessibility and helps to reach a broad range of participants across Member States.

The first virtual learning lab 'Introducing your microbiome', a free training course for secondary school science teachers, is currently running from 2 November to 7 December 2020. Its modular structure enables teachers to attend outside working hours. The course provides an overview of current human microbiome research and introduces bioinformatics as a tool in research. In its first week, the virtual learning lab was attended by around 100 highly committed participants from 29 countries.

Upcoming activities

44. Further confirmed virtual conferences and courses over the next months include:

2 Nov – 7 Dec:	ELLS Learning Lab: Introducing your microbiome
16–19 November:	EMBL Conference: From Functional Genomics to Systems Biology
23–27 November:	EMBL-EBI Course: Structural Bioinformatics
24 November:	EMBL Technology Day: Extracellular Vesicles: From Biology to Biomedical Applications
27–28 November:	22nd EMBL PhD Symposium: The Roaring 20s: A New Decade for Life Sciences
4–10 December:	EMBL Course: Design Thinking: Approaches for Chronic Disease Management
6–8 December:	EMBO Workshop: In situ Structural Biology: From Cryo-EM to Integrative Modelling
11–15 January:	EMBO Practical Course: Drosophila Genetics and Genomics
26–28 January:	EMBL Course: Exploratory Analysis of Biological Data: Data Carpentry
1–5 February:	EMBL-EBI Course: Single-Cell RNA-Seq Analysis using R
8–12 February:	EMBL Course: Deep Learning for Image Analysis
15–19 February:	EMBL-EBI Course: Next Generation Sequencing Bioinformatics
22–26 February:	EMBL-EBI Course: Introduction to Multiomics Data Integration and Visualisation
2–3 March:	EMBO | EMBL Symposium: Life at the Periphery: Mechanobiology of the Cell Surface
9–12 March:	EMBO | EMBL Symposium: Friend or Foe: Transcription and RNA Meet DNA Replication and Repair
16–19 March:	EMBL-EBI Course: Introduction to RNA-seq and functional interpretation
17–19 March:	EMBO | EMBL Symposium: Synthetic Morphogenesis: From Gene Circuits to Tissue Architecture
24–26 March:	EMBL Conference: VIZBI 2021: Visualizing Biological Data
26–30 April:	EMBL-EBI Course: Single-Cell RNA-Seq Analysis into Interpretation
17–20 May:	EMBL Conference: Chromatin and Epigenetics

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