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
Europäisches Laboratorium für Molekularbiologie

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Contents

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 4 March 2021, and will be updated as additional projects receive necessary safety and scientific approvals.

Update highlights

3. EMBL scientists have contributed critical expertise and provided collaborators with access to EMBL's state-of-the-art technology to better understand the novel coronavirus and find solutions to tackle the COVID-19 pandemic. Various research groups and scientific service facility teams have joined forces with external colleagues -- locally, nationally, across Member States and beyond.

   These close collaborations have been very fruitful, led to important insights into SARS-CoV-2 biology, and contributed to the development of new detection methods, mRNA vaccines, and the identification of potential COVID-19 treatments. The individual projects are summarised below and have been featured in a series of short videos (see items 14, 29, 32, 34, 36).

   EMBL-EBI has initiated an open letter in the hope to galvanise the international scientific community to show support for open sharing of SARS-CoV-2 data (see item 11)

4. EMBL supports the German state of Baden-Württemberg's sequencing initiative, which has been allocated € 31.5 million by the state to routinely sequence virus samples from the majority of newly diagnosed SARS-CoV-2 infections. The initiative is a vital tool in monitoring the prevalence and spread of novel and existing virus variants across Baden-Württemberg.

   EMBL Heidelberg's Genomics Core Facility contributes expertise in whole-genome analysis and carries out sequencing and data analysis of samples from the Rhine–Neckar region, in close collaboration with University Hospital Heidelberg and the German Cancer Research Center (DKFZ).

   EMBL's experience in setting up data infrastructures supports the rapid and efficient gathering, integration, and exchange of the generated data, regionally as well as internationally through existing

sequence databases, such as the COVID-19 Data Portal (see item 14). This will help in fighting the pandemic and provide crucial knowledge to better understand the emergence and spread of novel virus variants.

The joint activity involves EMBL and its partners in the Heidelberg–Mannheim Health & Life Science Alliance – Heidelberg University, DKFZ, University Hospital Heidelberg, University Hospital Mannheim – as well as the university clinics in Freiburg and Tübingen, the NGS Competence Center Tübingen of the German Research Foundation (DFG), and private laboratories. Combined sequencing capacities currently allow for the analysis of up to 8 000 samples per week. The initiative's set-up could serve as a blueprint for establishing similar infrastructures in other regions, now or in future pandemics.

5. EMBL-EBI scientists and colleagues have analysed the spread of the novel SARS-CoV-2 variant B.1.1.7 across the UK during the English national lockdown in November and December 2020. Their analysis confirms that B.1.1.7 is significantly more transmissible than previous strains and indicates that lockdown measures are less efficient in containing it.

   EMBL has provided a summary on the B.1.1.7 lineage in multiple languages. The note summarises epidemiological information about the spread of B.1.1.7 in the U.K. collated and in part conducted by researchers from EMBL-EBI. The note is for the information of researchers, public health authorities and governments. EMBL also utilised media connections to assist in the rapid dissemination of information about B.1.1.7 to public health officials, leading to significant coverage across Europe (see item 24).

6. EMBL scientists have established a robust protocol for the detection of coronavirus using next-generation sequencing, called 'Multiplexed SARS-CoV-2 Quantification' (McQ), which can process more than 5 000 samples in parallel. The procedure uses almost exclusively home-made enzymes and buffers and has been released as open science to make it widely accessible. An experimental weekly testing campaign has been implemented at EMBL sites in Heidelberg, Barcelona, Rome, and Grenoble, demonstrating the feasibility of centralised routine testing at a European scale (see item 25).

7. Scientists at EMBL Heidelberg performed a bioinformatic analysis of cell surface protein sequences to better understand how SARS-CoV-2 enters host cells. They identified a set of conserved protein motifs, which interact with other proteins involved in the uptake and processing of extracellular material. The analysis could inform the development of novel treatments to slow down SARS-CoV-2 infection (see item 26).

8. EMBL-EBI scientists have integrated drug target information with SARS-CoV-2 screening data and large-scale genetic analysis to identify gene targets associated with the risk of COVID-19 hospitalisation. Existing drugs that act on these targets might be repurposed to meet the urgent need for therapeutics against COVID-19 (see item 27).

9. Scientists at EMBL Hamburg collaborated with colleagues from biotechnology company BioNTech, using biological small-angle X-ray scattering (SAXS) to study nanoparticles that serve as vehicles for mRNA vaccines. The analysis helped to develop concepts on how to further improve formulation development (see item 38).

10. Several COVID-19-related research projects have been summarised in preprints or published as open-access publications (see items 19–20, 24–27, 29–30, 32, 34–37, 42–44).

TOP

Calls to action

11. The quick and easy international sharing of SARS-CoV-2 data, particularly sequence data, is helping researchers to understand the virus and the disease, monitor its spread and develop treatments and vaccines. EMBL-EBI has initiated an open letter in the hope to galvanise the international scientific community to show support for open sharing of SARS-CoV-2 data. The open letter, hosted on the COVID-19 Data Portal website, has already been signed by hundreds of researchers. We hope that you will show your support to the cause by joining the list of signatories.

12. EMBL is asking its Member States for contacts to COVID-19 serology and seroprevalence 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.

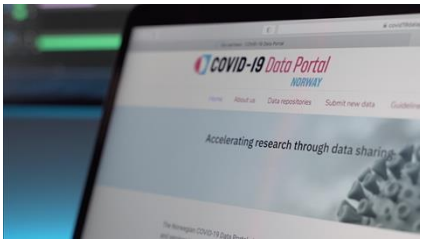
13. EMBL-EBI scientists are following with interest wastewater testing as a means to track the spread of coronavirus and consider establishing a data sharing group for this purpose. We encourage feedback from Member States on the extent of ongoing testing activities, to explore whether the development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

TOP

Services for Member States

14. 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



Video 1: *The COVID-19 Data Platform: A growing ecosystem.* (*external link*)

- 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.

Video 2: *Extending the COVID-19 Data Platform: new tools and services. (external link)*

In 2020, the COVID-19 Data Portal recorded over 3.6 million web requests by around 114 000 users from 175 geographical locations, including most of the European countries. Close to 550 institutions from 49 countries have deposited data and the Portal currently offers open access to over half a million data records.

Improved phylogenetic visualisation has been added to the COVID-19 Data Platform and 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.

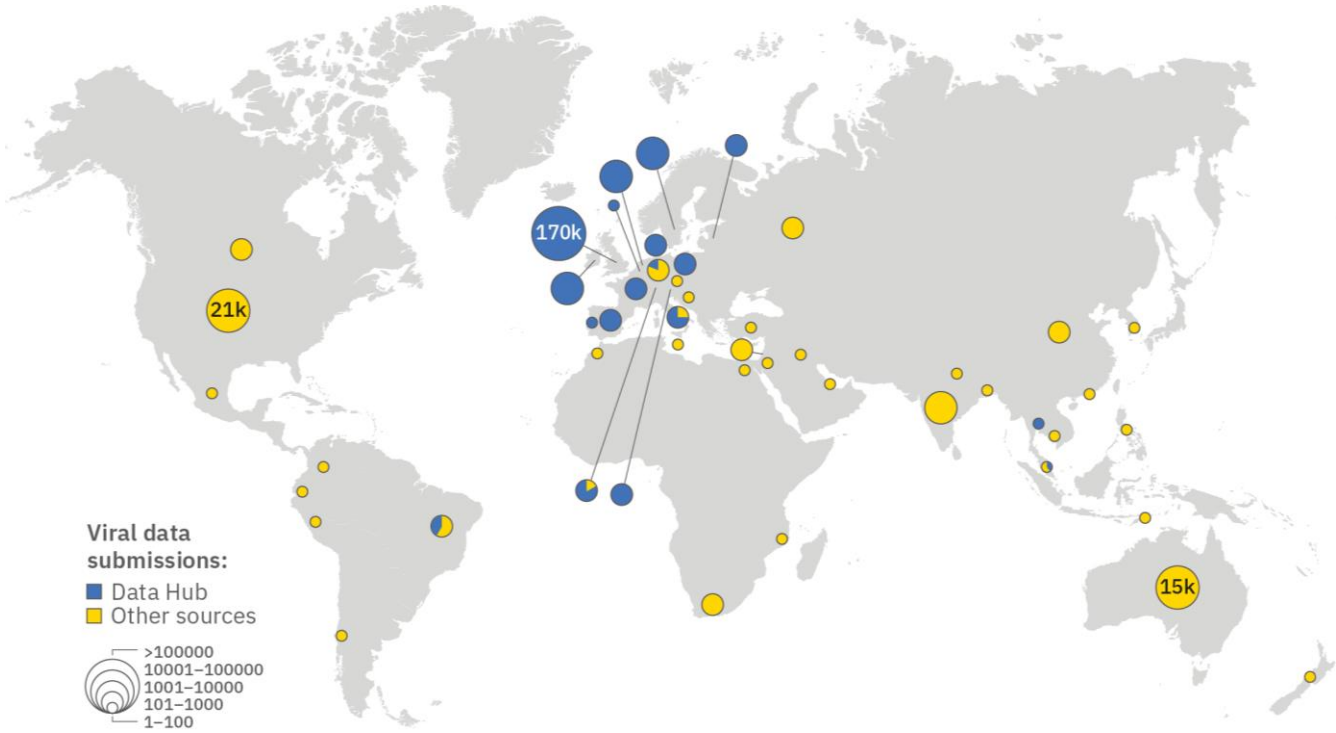


Figure 1: *World map of raw viral data submissions. 'Other sources' include sequences submitted via the International Nucleotide Sequence Database Collaboration (see main text). Date: 26 January 2021.*

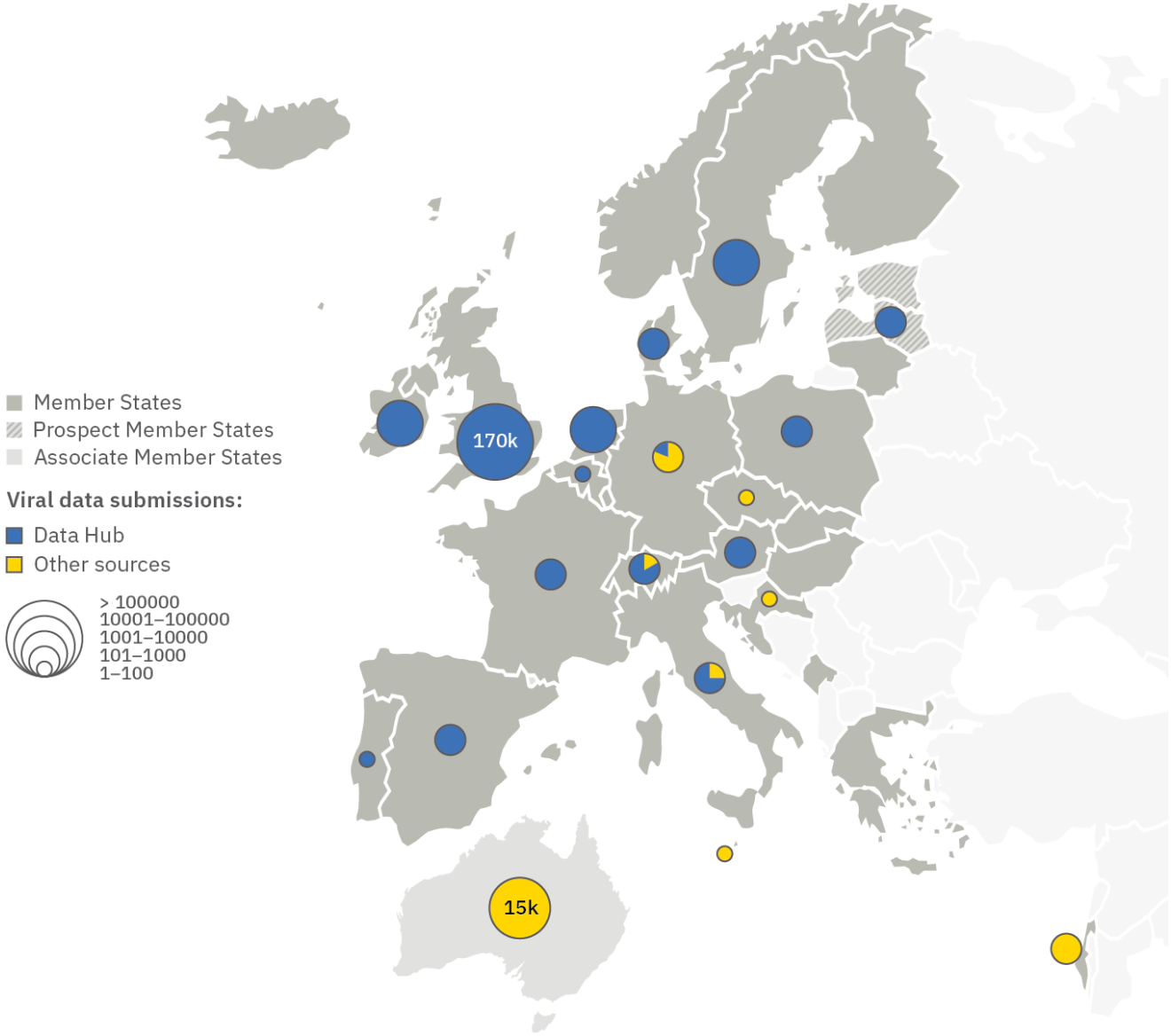


Figure 2: *Contributions of raw viral sequence data from Member States. 'Other sources' include sequences submitted via the International Nucleotide Sequence Database Collaboration (see main text). Date: 26 January 2021.*

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 16 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. The first COVID-19 metabolomics set has been deposited into the EBI metabolomics database Metabolights.

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 now offers access to indexed COVID-19 preprints, including information on COVID-19-related funding grants to make the information more widely available and accessible.

15. 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.

16. 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 six submissions totalling 4.4 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.

17. 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.

18. 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.

19. 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 39).

Together with ESRF, EMBL has restarted the activities of the Joint Structural Biology Group in Grenoble to support coronavirus-related projects. A new initiative allows 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. It enables a streamlined process through crystal production, testing, and data collection. The high automation of HTX and the MASSIF beamline are unique and very valuable to support structural biology projects in conditions of confinement.

Since the JSBG beamlines came back for user operation in August, they have automatically processed over 5 500 samples on MASSIF-1, including 500 COVID-related user samples, such as crystals of SARS-CoV-2 protein targets for drug discovery. EMBL scientists have been involved in a study that screened antibody repertoires of hospitalised COVID-19 patients and employed the MASSIF-1 beamline for structural characterisation of antibodies. The results are available as a preprint and the manuscript has been submitted for peer-reviewed publication.

20. 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. Both macromolecular crystallography (MX) beamlines at EMBL Hamburg are operating for remote user access. EMBL scientists have been involved in the project 'Massive X-ray screening against the SARS-CoV-2 main protease' – a collaborative effort by more than 100 scientists at EMBL, DESY,

Hamburg University, and the Heinrich-Pette-Institute. In the context of this project, more than 700 diffraction data sets on SARS-CoV-2 main protease (MPro) protein crystals were collected at EMBL's MX beamlines to identify compounds that could act as potential new drugs.

Selected candidate compounds then underwent further characterisation in EMBL's SPC Facility. EMBL scientists performed detailed biophysical characterisation of the interaction of these compounds with the viral protease. The results have been made available as a preprint and are currently under peer review.

The SPC Facility has also performed biophysical characterisation and optimisation experiments on another SARS-CoV-2 protease (PLPro) and two non-structural proteins (nsp7+8) to support structural studies. They are currently investigating the binding of MPro and PLPro to different potential binders, mainly small molecules.

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 scientists are currently searching for inhibitors for the spike protein's interaction with the cellular ACE2 receptor, using computational and biophysical tools, in collaboration with the Mass Spectrometry Facility at EMBL Hamburg.

The SPC facility was also involved in the identification of synthetic antibodies against SARS-CoV-2 (see item 32).

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 38).

21. 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 36). 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.

22. 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 25), 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

23. 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 described below 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.

24. Understanding the spread of novel SARS-CoV-2 variant B.1.1.7
Scientists at EMBL-EBI and at the Wellcome Sanger Institute have performed a thorough analysis of daily local SARS-CoV-2 incidence data and weekly genomic surveillance data from the COVID-19 Genomics UK Consortium, to better understand the spread of the novel SARS-CoV-2 variant B.1.1.7. The scientists investigated lineage-specific growth of B.1.1.7 and other strains during the English national lockdown from 5 November – 2 December 2020.

    Their analysis confirms that B.1.1.7 is significantly more transmissible than previous strains, spreading across the UK during the lockdown with an average R value of 1.25, while other virus variants contracted at average R values of 0.85 in most regions.

    The results indicate that lockdown measures are less efficient in containing incidence of the B.1.1.7 strain, as compared to previous lineages. The preliminary report has been made available in the influential online epidemiology forum *virological.org*. The study has been directly influential in informing governments and public health authorities in the United Kingdom, France, Germany, Israel, and India.

    EMBL has provided a summary of the current knowledge about the B.1.1.7 lineage in multiple languages on its website and shared it with local stakeholders and media outlets. The study offered an opportunity to establish many new contacts with key media players and scientific partners across Member States. EMBL-EBI group leader Moritz Gerstung, lead scientist on the study, and EMBL-EBI Director Rolf Apweiler were interviewed by German TV channels (*Das Erste*, *ZDF*, *RTL*, *ntv*), *Le Figaro*, the *Polish Press Agency PAP* (covered on various outlets, including *TVP*, *medonet*, and *interia*), and

Czech online news portal *seznamzpravy.cz*. Further interviews with EMBL scientists, including group leader Maria Bernabeu from EMBL Barcelona, have been requested or conducted.

25. 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 SARS-CoV-2 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 22) and non-proprietary buffers. This drastically reduces costs for testing, makes it accessible to a wider range of institutions worldwide, and avoids 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 the EMBL sites in Heidelberg, Barcelona, Rome, and Grenoble, to test the applicability of McQ for regular population-scale testing and compare its performance with other technologies. More than 1 800 samples have been processed, adding to further refinement of the testing procedures. A manuscript describing the McQ protocol has been made available as a preprint. The approach demonstrates the feasibility of centralised routine testing at a European scale. In future, McQ could help scientists and clinicians to regularly test large parts of the population.

26. Understanding how SARS-CoV-2 enters host cells
The ACE2 cell surface protein mediates SARS-CoV-2 infection, but the molecular mechanisms that support viral entry into host cells are not well understood. It has now become clear that ACE2 shows very little expression in lung and therefore it is assumed that SARS-CoV-2 binds to additional cellular proteins, such as integrins and also, as recently demonstrated, Neuropilin-1 to infect host cells.

Scientists at EMBL Heidelberg performed a bioinformatic analysis of ACE2, integrin and neuropilin-1 protein sequences. They identified a set of short linear motifs (SLiMs) – stretches of amino acids, the proteins' building blocks – which are part of ACE2 and integrins and could facilitate viral infection. SLiMs interact with other proteins and thereby influence various cellular processes.

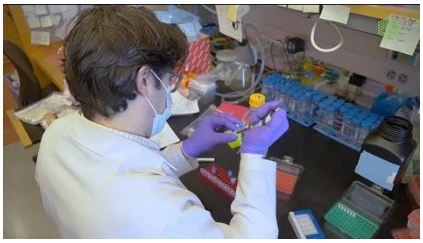
Colleagues at Uppsala University in Sweden then performed in vitro experiments using protein fragments and confirmed that several of the identified SLiMs interact with proteins involved in endocytosis and autophagy – cellular pathways that mediate the uptake and processing of extracellular material. The findings open the way to cellular studies to test whether integrins can bring viral material to the autophagosomes, which share components with the double membrane vesicles (DMVs) characteristic of viral replication sites. Both studies were published in *Science Signaling*, and the research received wide media coverage in Argentina (e.g. *lavoz.com.ar*, *pagina12.com.ar*, *baenegocios.com*), where one of the scientific collaborators is based. The findings could inform the development of novel treatments to slow down SARS-CoV-2 infection in COVID-19 patients.

27. Identifying potential COVID-19 drug targets
Drug repurposing provides a rapid approach to meet the urgent need for therapeutics to address COVID-19. EMBL-EBI scientists, in collaboration with the US Veterans Administration Million Veteran Program, have integrated drug target information from the chemical biology bioactivity database ChEMBL with SARS-CoV-2 screening data and large-scale genetic analysis to identify actionable targets associated with the risk of COVID-19 hospitalisation.

The scientists analysed more than 1 200 actionable genes that encode protein targets for which approved drugs or drugs in clinical development exist. By combining genetic data from over 7 500 hospitalised COVID-19 patients and more than 1 million controls, the researchers identified two genes – Interferon alpha/beta receptor 2 (IFNAR2) and Angiotensin converting enzyme 2 (ACE2) – and their proteins as promising drug targets. The results recommend prioritisation of clinical trials to evaluate the efficacy of drugs against these targets in COVID-19 patients. The study has been made available as a preprint.

28. 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.

29. 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.



Video 3: *The search for COVID-19 treatments. (external link)*

Clinical trials for five compounds have been launched 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. Clinical trials for another 21 of the identified compounds have been launched.

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.

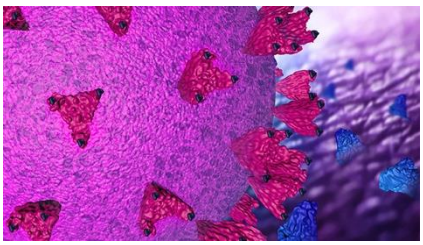
EMBL-EBI scientists continue to be heavily involved in follow-up work to these three studies.

30. 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 has been summarised in a preprint and published in *BioEssays*. It 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.

31. 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.

32. 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.



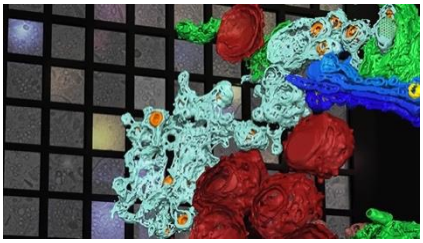
Video 4: *International collaboration identifies a mini-antibody to combat COVID-19. (external link)*

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)*.

33. 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.

34. 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.



Video 5: *Replication of the coronavirus in 3D. (external link)*

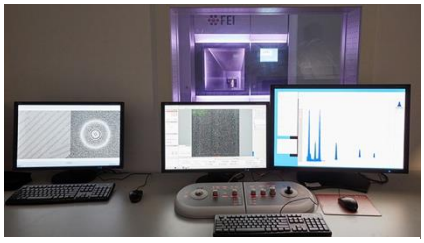
EMBL scientists performed a full study of infected cells, including transmission electron microscopy, electron tomography, and focused ion beam scanning electron microscopy (FIB-SEM) of cells at different time points post-infection. The analysis revealed the role of cellular organelles in virus replication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

35. 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.

36. 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.



Video 6: *EMBL's infrastructure and expertise shed light on the ability of SARS-CoV-2 to infect cells. (external link)*

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).

37. 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 28), 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. The study is available as a preprint and has been published in *Molecular Systems Biology*.

38. 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 32; published). 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 being analysed).

    Further, an extensive collaboration was established with German biotech company BioNTech, the developer of one of the first approved anti-coronavirus vaccines based on messenger RNA (mRNA). Three papers were published in 2020 on the SAXS studies of hybrid nanoparticles from lipid and polymeric components, which serve as vehicles for mRNA vaccines. These studies presented the concepts on how to further improve the formulation development for mRNA-based vaccines. The results are also useful for the fine-tuning of tailored mRNA delivery systems.

39. 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 19) 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.

40. 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. The first critical site of the ACE2 gene has been successfully edited and the scientists are now targeting the other critical points in different parts of the gene.

41. 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.

42. 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 published in *Nature Reviews Genetics*. So far, the database has been accessed by over 1 150 unique users from 53 different countries and has been mentioned in six 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.

43. Distinguishing coronavirus genome mutations from inadvertent errors
Scientists at EMBL-EBI have performed a large-scale analysis of over 140 000 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. The work has been made freely available via the influential online epidemiology forum *virological.org*, and has subsequently been incorporated into a collaborative publication with colleagues at the University of California Santa Cruz in *PLOS Genetics*.

44. 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

45. 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. In 2020, 17 conferences / symposia and 16 courses were offered online by the EMBL International Centre for Advanced Training (EICAT) with the Course and Conference Office (CCO), EMBL-EBI Training and EMBL Hamburg, which attracted a total of 9 869 participants of over 125 nationalities residing in 102 countries, including around 500 virtual chairs and speakers. Upcoming virtual conferences and courses are listed under item 49.

External Training has also launched a new online learning platform, 'EMBL eCampus', and EMBL-EBI is in the final stages of launching their EBI-Academy online learning platform. In addition, External Training has implemented a virtual social programme, and offer fee waivers and childcare grants for virtual events. A total of 587 fellowships and fee waivers were granted to virtual event participants in 2020. In addition, virtual event platforms have been tested in order to find the best format for EMBL-organised conferences. One of these platforms will be used for seven virtual conferences in the first half of 2021.

46. The EMBL International PhD programme and Internal Training have moved their recruitment, training, and career development activities towards virtual formats. This includes the EMBL Career Webinars that have attracted over 2 100 attendees so far, 61% of whom are based at other institutions across Member States.

47. 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'.

    The members of the Partnership for Structural Biology Grenoble - EMBL, Institute Laue-Langevin (ILL), European Synchrotron Radiation Facility (ESRF), and Institut de Biologie Structurale (IBS) - in collaboration with the Institute for Advanced Biosciences (IAB), have launched a new "Host-Pathogen Interactions Club" (www.hostpathogen.fr).

    The club aims to promote networking among local researchers through half-day scientific meetings, covering and reflecting the broad range of pathogens (viral, bacterial, parasitic, fungal) and host defence mechanisms. It was launched on 10 December 2020 with a virtual kick-off meeting on COVID-19. The meeting gathered 131 participants connecting mainly from France, but also from the United Stated, Lebanon and Sweden.

48. 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 was run with around 100 Greek students in mid-November, closing the programme's pilot phase. Upcoming slots for Virtual School Visits in 2021 can be found on the ELLS website. 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

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

9–12 March:	EMBO | EMBL Symposium: Friend or Foe: Transcription and RNA Meet DNA Replication and Repair
16–19 March:	EMBL 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
29–30 March:	Workshop: Strategy for future EMBL research infrastructures in the Life Sciences in Hamburg
31 Mar – 12 May:	Online Course: SAXS (Small-Angle X-Ray Scattering) for Biomolecules
12–19 April:	EMBO Practical Course: Microbial Metagenomics: A 360° Approach
26–30 April:	EMBL Course: Single-cell RNA-Seq & Network Analysis Using Galaxy and Cytoscape
3–7 May:	EMBO Practical Course: Quantitative Proteomics: Strategies and Tools to Probe Biology
4–7 May:	EMBO | EMBL Symposium: The Identity and Evolution of Cell Types
17–20 May:	EMBL Conference: Chromatin and Epigenetics
17–21 May:	EMBL Course: Cancer Genomics
17–25 May:	EMBO Practical Course: Measuring Translational Dynamics by Ribosome Profiling
18–20 May:	EMBL Course: Managing a Bioinformatics Core Facility

25–27 May:	EMBL Conference: BioMalPar XVII: Biology and Pathology of the Malaria Parasite
14–16 June:	EMBO Workshop: Predicting Evolution
15–17 June:	EMBL Course: Bioinformatics for Principal Investigators
21–25 June:	EMBL and Wellcome Genome Campus Joint Course: Systems Biology: From Large Datasets to Biological Insight
28 June – 2 July:	EMBO Practical Course: Advanced Methods in Bioimage Analysis
28 June – 2 July:	EMBL and Wellcome Genome Campus Joint Course: Summer School in Bioinformatics
7–9 July:	EMBO | EMBL Symposium: New Approaches and Concepts in Microbiology
26–30 July:	EMBO Practical Course: FISHing for RNAs: Classical to Single Molecule Approaches

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