



## FORTH's responses to COVID-19 pandemic

The Foundation for Research and Technology-Hellas (FORTH) and its Institutes have been made available to the State and Public Health Authorities, in order to contribute to the common effort to address the pandemic of COVID-19, with their top-level infrastructure and expertise. Specifically,

### INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY

The Institute of Molecular Biology and Biotechnology (IMBB) of FORTH in Heraklion, is actively pursuing a number of research activities related to COVID-19 disease. The specific actions include:

- 1) Research towards better understanding the molecular mechanisms of COVID-19 disease pathogenesis with emphasis on the mechanisms of pathological activation of macrophages. Severe COVID-19 is caused by the uncontrolled activation of macrophages through the release of a cascade of pro-inflammatory cytokines. The molecular mechanisms of the disease pathogenesis are unknown. Our efforts are focused on the mapping of immunometabolic disorders in cells of endogenous and acquired immunity in COVID-19 patients. The study will contribute to the development of biomarkers for disease staging and targeted immunomodulatory therapies.
- 2) Study of mechanisms of regulation of cytokine storm and therapeutic possibilities. The aim of the work is to clarify the importance of the SARS-CoV2 / ACE2 interaction in monocytes and macrophages and how it contributes to the cytokine storm and the deregulation of coagulation. As a tool we will use a pseudovirus carrying SARS-CoV2 Spike, as we did in the past for MERS-CoV (Oncotarget, 2017, 8: 9053). The results will highlight the importance of the Spike / ACE2 interaction suggesting therapeutic approaches.
- 3) Platform for the development of inhibitors for SARS-CoV-2 coronavirus. The IMBB Structural Biology team has developed technologies for the development of SARS-CoV-2 coronavirus peptide inhibitors. Inhibitors have structural elements from the protease domain of the ACE2 enzyme, which form extensive interactions with the receptor binding domain (RBD) domain of the virus. Inhibitor elements are structurally stabilized by a specially designed 4- $\alpha$ -helix bundle protein scaffold. The aim is to develop, characterize and test for RBD binding of 2-3 inhibitors against SARS-CoV-2 using the new  $\alpha$ -helical protein scaffold platform.
- 4) Having available a modern genomic analysis infrastructure (FORTH is a hub of the National Networks of Medical Precision / Personalized Medicine and operates the only laboratory of Ancient DNA Analysis in the country), IMBB is in place to perform deep analyses the genetic material of the virus, so that and to trace the origin of the virus. The information obtained will be extremely useful for the characterization of the different forms of the virus in the Greek territory, but also for the determination of their geographical origin.
- 5) Study of molecular evolution of SARS-CoV-2 virus and host-virus interaction. We use population genetics methods to estimate the parameter values related to the modern evolution of the virus. Parallel activity involves mapping the transcriptome and epigenome to the host cells before and after remission of disease symptoms. The research will contribute to the understanding of the mechanisms of pathological response and the emergence of new bio-indicators for the prognosis of the disease.

- 6) Production of real time RT-PCR reagents for the molecular diagnosis of the virus. The MINOTECH-IMBB laboratory has the ability to produce more than 1,000,000 units / month of the enzyme Taq DNA polymerase and more than 10,000,000 units / month MMLV Reverse Transcriptase at low cost. All the processes of MINOTECH Biotechnology are adapted to the instructions of ISO 9001: 2008. The above enzymes are key components of SARS-Cov2 virus PCR detection methods. MINOTECH-IMBB is the only laboratory in Greece with enzyme production activity.
- 7) Evaluation of innovative methods for detecting SARS-CoV-2 directly in patient samples or with isolated RNA at points of interest (point-of-care). IMBB-FORTH Biosensors laboratory has developed portable genetic biomarker detection systems (see below) and a SARS-CoV-2 molecular detection protocol. The aim is to evaluate the method in patient samples. The results of the evaluation will be used to formally certify the method for detecting COVID-19 at point-of-care by a certified inspection body (EU-IVDR).
- 8) A new innovative method of molecular diagnosis, which is performed outside a specialized laboratory, at the location of the patient or the sample to be analyzed, was developed by the Biosensors laboratory of IMBB of FORTH (<http://biosensorslab.biology.uoc.gr/>). The method uses an innovative portable device made with 3D printing and smart phone, provides fast resolution, within 30 minutes' maximum, is characterized by easy-to-use protocol, allowing use by non-specialized personnel, and low cost so it can be used in developing countries. Clinical evaluation with patient samples for the detection of infectious diseases (COVID-19) and cancer mutations (BRAF V600E) showed that the method gives comparable results <https://www.biorxiv.org/content/10.1101/2020.07.22.215251v11> with the corresponding laboratory techniques. BIOPIX DNA TECHNOLOGY P.C. (<https://biopix-t.com/>), FORTH's spin-off company, was founded in December 2019 with the aim of providing molecular diagnostic tools to those who need them, regardless of their financial ability, country of residence and level of education. The company maintains close ties with FORTH through the exclusive use of the respective patent, as well as with the University of Crete and the Science Park of Patras. BIOPIX-T is in the process of completing the 1st round of financing (1.2M €) from business and private funds, in order to place on the market, the pioneering molecular analysis device under the brand name "IRIS". The company has already entered into a commercial agreement to promote the SARS-CoV-2 detection test in Europe, the USA and sub-Saharan Africa.
- 9) In the final phase to receive EOF certification are the two diagnostic tests for the coronavirus developed by EnzyQuest, the Greek startup, which recently received funding of 400,000 euros from Uni.Fund. It is an innovative start-up company that operates in the field of enzyme biotechnology and is a spin-off of the Institute of Technology and Research (FORTH).

#### **INSTITUTE OF MOLECULAR BIOLOGY & BIOTECHNOLOGY – BIOMEDICAL RESEARCH DEPARTMENT**

The Department of Biomedical Research (DBR) of FORTH at Ioannina can offer equipment and infrastructure for molecular identification (RT-PCR) of the SARS-COV2 virus, as well as expertise and supervision for the establishment of diagnostic tests in appropriately designated areas (e.g. hospitals, etc.), using certified diagnostic tests.

- 1) The Institute of Computer Science (ICS) in FORTH, Heraklion, in collaboration with IMBB, performs bioinformatics analysis of patients' genome as well as the whole genome of SARS-CoV-2 to detect associations between viral mutations and polymorphisms in the human genome that may affect the disease prognosis. ICS researchers have already developed computational pipelines to perform such analyses. Furthermore, researchers from the Computational BioMedicine Laboratory (CBML, ICS), in two recent studies reposted in bioRxiv, have analyzed the full genome of SARS-CoV-2 and they have inferred the time point it was introduced in the human population, genomic regions on which natural selection has operated in the recent past, and recombination events (<https://www.biorxiv.org/content/10.1101/2020.04.21.054122v1>). Also, they have examined the exploitation of phylogenetic-based analysis of SARS-CoV-2, highlighting potential difficulties in such analyses (<https://www.biorxiv.org/content/10.1101/2020.08.05.239046v1>).
- 2) The Computational Biomedicine Laboratory has developed a number of AI models aiming to improve the early detection of COVID directly from routine medical imaging examinations. In particular, two models have been developed and published in scientific journals, one based on X-ray and one on CT data which are constantly being improved as new COVID examination data are being shared worldwide. ICS-FORTH was recently awarded a gold Healthcare Business Award (2020) for the abovementioned work regarding the AI system for COVID detection from medical images.
- 3) The Human-Computer Interaction Laboratory has developed the '@HOME' system for remotely monitoring COVID-19 patients who do not require hospitalization, during their stay at home. @HOME offers to patients a very simple and user-friendly smartphone application, and to medical teams a desktop application. Through the mobile application, patients receive reminders and exchange messages with the medical team, while they also have access to official information about COVID-19. The medical team can continuously monitor the health condition of all registered patients and can be alerted to react promptly, when an emerging situation requires intervention. @HOME has been implemented in the context of Ambient Intelligence Programme of ICS.
- 4) The Information Systems Laboratory, through the CAPrice Initiative (<https://www.caprince-community.net/>), is offering the CAP-A platform (<https://isl.ics.forth.gr/cap-a-portal/>) for raising awareness and mobilising citizens in matters related to the protection of privacy by mobile applications. Building on crowdsourcing and collective intelligence methodologies, the platform enables the monitoring of proper privacy policies of mobile software applications for proximity and digital contact tracing of COVID-19 infected individuals. This initiative was also offered to the Pan-European Privacy-Preserving Proximity Tracing (PEPP-PT) Initiative, with the aim to quickly inform users of the features and characteristics of such applications.
- 5) The Center for eHealth Applications and Services (CeHA) of FORTH-ICS provides technical support services to COVID-19 reference hospitals (General Hospital of Elefsina "Thriassio", Pammakaristos Hospital, University Hospital of Patras, etc.).
- 6) The Center for eHealth Applications and Services has developed the Integrated Care Solutions (ICS) software suite, which consist of more than 120 applications, operating productively since 2000 supporting the daily operation of a large number of health units, serving thousands of citizens. Individual applications are utilized in the international market. At the hospital setting, ICS is used by administrative, medical and nursing staff to manage patients and to support integrated care. ICS is interconnected with third party systems (such as those from EOPYY, IDIKA, Ministry of Health, etc.) supporting the automation of the administrative and medical workflow (ordering laboratory tests and receiving results, sending data, providing EOPYY services,

interconnection with the ATLAS system of IDIKA , etc.), as well as the prompt delivery of effective health care at the point of need.

- 7) The Center for eHealth Applications and Services (CeHA) has developed the platform "Safe in COVID-19" (<https://covid19.forthehealth.gr/>) an outbreak response tool, designed to effectively track suspect, probable and confirmed incidence cases in a pandemic by means of a mobile app used by citizens to provide immediate feedback. "Safe in COVID-19" is developed based on an already existing personal health record app, which has been extended to properly accommodate specific needs that emerged during the crisis. The aim is to better support human tracers and should not be confused with proximity tracking apps. It respects safety and security regulations, while at the same time it conforms to international standards and widely accepted medical protocols. Part of the platform has already been activated at FORTH, already since October 21, 2020, when the implementation of a research project aimed at the molecular detection of SARS-CoV-2 virus in samples from volunteer workers who do not show symptoms of active infection began. A special adaptation of the "Safe in COVID-19" digital platform is used to assist in carrying out the research. The platform allows, among other things, the electronic scheduling of examination visits for rapid detection of coronavirus by the employees themselves, the management of appointments by authorized personnel as well as the sampling of employees in a way that fully ensures the secure management of anonymous data. The application has been developed by the CeHA of FORTH-ICS, which implements an information security management system certified according to ISO 27001:2013. Related references: [https://covid19.forthehealth.gr/?page\\_id=790](https://covid19.forthehealth.gr/?page_id=790) (application presentation page), <http://ebooks.iospress.nl/publication/55440> (pHealth scientific publication). This work has already been presented at three international scientific conferences (17th International Conference on Wearable Micro and Nano Technologies for Personalized Health, 20th IEEE International Conference on BioInformatics And BioEngineering, 3rd International Workshop on Semantic Web Meets Health Data Management), and has already been scheduled for publication in an international scientific journal (IEEE Transactions on Bioengineering & Bioinformatics) following the acceptance of a relevant invitation for submission.

#### INSTITUTE OF CHEMICAL ENGINEERING SCIENCES

- 1) The Institute of Chemical Engineering Sciences (ICE-HT) is highly active in the investigation of the airborne transmission of the SARS-Cov-2 virus. Two of its collaborating faculty members participated in the international team of scientists, who recently published a study urging the World Health Organization (WHO) to consider the airborne transmission as a major infection route (<https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa939/5867798>). The letter of the experts to WHO had a significant impact, as it led the Organization to acknowledge the possibility of the airborne transmission of the virus, and accordingly modify its recommendations on the necessary COVID-19 precaution measures (<https://www.who.int/publications/i/item/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations>).
- 2) The ICE-HT Laboratory of Composite and Nanostructured Materials and the Laboratory of Nanotechnology and Advanced Materials of the Department of Chemical Engineering, University of Patras with the participation of the spin-off company ADRINE at the Patras Science Park produced 3D-printed Face Shields and delivered them to the University General Hospital of Patras, the Karamandaneio Children's Hospital of Patras and the Hospital of Lemnos. The manufacturing process involves the 3D computer design of the product based on the actual needs regarding functionality, preparation time, and performance.

- 3) Several ICE-HT labs have collaborated for the conduction of a series of laboratory experiments for the testing of candidate materials for face masks and protective clothing of health staff.
- 4) The ICE-HT Metabolic Engineering and Systems Biology Laboratory, in collaboration with the First Pediatric Clinic of the Medical School, University of Athens and the Children's Hospital "Agia Sofia" consider the initiation of a collaboration on the metabolomic analysis of biological samples from children diagnosed with COVID-19 and/or Kawasaki disease. This method will be used to investigate whether there is a distinct metabolic profile of children with COVID-19 which could be used as a diagnostic tool and study the molecular pathophysiology of the disease in both sexes for more specialized treatments, as well as to examine a possible connection of COVID-19 with Kawasaki disease.
- 5) In general, ICE-HT has advanced expertise for the analysis of the profile of small molecules (metabolomics) in samples of biological fluids of patients (blood, urine, saliva) at various stages of the disease, for the investigation of diagnostic biomarkers, but also for the analysis of the impact that the infection has on the patients' metabolism, in the context of their underlying medical condition.
- 6) During the first wave of the pandemic, the use of cell therapies (mainly using mesenchymal stem cells, MSCs) has been explored as a means for treating the 'acute respiratory distress syndrome', which has been responsible for a large portion of virus-related deaths. Under pandemic conditions with the increased burden of clinical centers, the production of such products with the existing manual methods is challenging. At FORTH/ICE-HT, existing know-how on bioreactor technologies is available to allow the automated production of such cellular products, as well as metabolomics technologies for their certification. This will reduce significantly the needs for human resources, while a consistent production line and high-reliability cellular products will become available for patients with severe symptoms.
- 7) ICE-HT has also the required expertise for the development of Dipstick Tests for molecular identification of SARS-CoV-2 and for antibody detection.

#### INSTITUTE OF ELECTRONIC STRUCTURE AND LASER

- 1) The Institute of Electronic Structure and Laser (IESL) of FORTH in Heraklion has been engaged in the construction of Face Shields with Additive Manufacturing (3D Printing) techniques that have been offered to the 7th Health District of Crete, to be used in local hospitals and schools, as well as to the Medical School of the University of Crete. We are always at the disposal of the Authorities for additional shields.
- 2) IESL is involved with the development of photocatalytic materials, which are capable to that have the ability to decompose gaseous pollutants, fight bacteria and destroy viruses with the help of visible light; thus, they are able to significantly improve the quality of the inhaled air. The advantage of the technology is that it can be applied indoors, such as in hospitals, schools, hotels, biological stations, nursing homes, etc. Their action is long-lasting and effective in combating diseases related to the upper respiratory system, such as asthma and bronchitis. They are particularly effective in the degradation of pathogenic microorganisms such as *Staphylococcus Aureus*, *Klebsiella Pneumoniae*, *Escherichia Coli (E-Coli)* and *MS2 Bacteriophage* in liquid waste, thus, contributing to fight against nosocomial infections and the wastewater treatment.
- 3) Moreover, the company PCNano Materials IKE, a spin-off company of IESL-FORTH, which was recently established with funding from the European Investment Fund through the VC "Big Pi", proceeded to the production of face masks with antibacterial coating. The masks are enriched on their outer surface with antibacterial coating, the action of which lasts as long as this coating is present on the surface.

The Institute for Mediterranean Studies (IMS-FORTH), based in Rethymnon, provides the following initiatives:

Geophysical Actions

- Research on the reduction of heat emission in urban complexes of Greece and Crete as well as worldwide during the pandemic.

Historical Actions

- Pandemics, and especially plague, in the Ottoman Empire.
- Medical and “magical” approaches and interpretations of diseases.
- Impact of epidemics/pandemics on the economy of the Greek state in nineteenth and twentieth centuries.
  - Health and economic policy of the Greek state in nineteenth and twentieth centuries.
  - Public health policies on the urban centers of the Greek state.
  - Epidemics and the occupational morbidity in the Greek industry.
  - Greek medical Press in nineteenth and twentieth centuries. Recording of publications, relevant articles and contributors.
  - Cemeteries and public health. {Collaboration of historians with art historians}
  - Disease in the ecclesiastical discourse.
  - Venereal diseases, prostitution and public health in the nineteenth and twentieth centuries’ Greek state.
  - Health professionals/social history of healthcare professions (doctors, nurses, pharmacists): education, military recruitment, professionalization, labor regimes, collective actions, claims etc.
- Representations of pandemics in the modern and contemporary art history.
- Representations of pandemics in theater, cinema and literature.