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COVID-19 and the value of knowledge

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The health emergency caused by COVID-19 has resulted in rapid and profound changes in our way of life, the medium- and long-term consequences of which remain unclear. The Margarita Salas Center for Biological Research, like society as a whole, has been impacted by the pandemic, which has affected our staff and their families, as well as the centre's activity. However, we have refused to resign ourselves to this situation, as is made clear in this issue of the newsletter of the CIB Margarita Salas. In this issue, we wish to highlight the response to the pandemic of our research groups, which, like many other laboratories, have put their knowledge to work in the fight against COVID-19. The last few months have seen a dramatic increase in the amount of scientific information published in the media and circulated on social networks, in many cases provided directly by researchers themselves. This has been highly motivating. Private donations from individuals, businesses and organizations to fund projects related to the pandemic have also increased significantly in Spain. But, once the health emergency is over, will we return to the previous situation whereby public appreciation of researchers is not matched by public or private financial support for science? More worryingly, although society has realised the importance of research to combat COVID-19, will we return to a situation whereby Spanish society feels we should simply rely on research done in other countries?

Because when scientists highlight, with little success, the value of knowledge, it is precisely this that we refer to: our ability to respond quickly to a very new situation. Knowledge is an intangible thing that, under normal conditions, is converted little by little into services and products that are useful for society at large or for companies that fund the research. This fact is well understood and exploited by countries and companies that are world leaders in research, technology, and economics, but has not yet percolated into Spanish society. Services and products are the applications of research, the tip of the iceberg under which the rigorous and time-consuming work of knowledge gathering is hidden. This knowledge base, spread across our research centres, is precisely what we are now re-orienting to the development of vaccines and antiviral treatments, and the discovery of new ways to fight COVID-19.

The creation of the Global Health Interdisciplinary Platform by the Spanish National Research Council (CSIC), also discussed in this issue, is an appropriate response that highlights the importance of a multidisciplinary approach to solving complex problems. This platform seeks to put to use all the treasured knowledge, acquired not only in the fields of virology and immunology, but through a variety of research projects in different fields. These include biomedicine, medicinal chemistry, genetics, bioinformatics, artificial intelligence, engineering, new materials, economics, and demography. Using this coordinated knowledge, we will fight this pandemic and those that may occur in the future. In the globalized world in which we live, potential threats and their scope are unpredictable: COVID-19 has made this very clear to us.

Finally, I would like to hightlight other modest but relevant recent contributions of the CIB Margarita Salas: donation of our personal protective equipment (PPE) to healthcare personnel at the Hospital Infanta Sofía (San Sebastián de los Reyes, Madrid); 3D printing of face protection masks for healthcare workers; adaptation of a PCR protocol to enable collaboration in the diagnosis of COVID-19; and the willingness of our researchers to meet society's demands for information.

The Global Health Interdisciplinary Platform: a strong commitment

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One of the features of scientific research since the emergence of the new SARS-CoV-2 coronavirus and the declaration of the COVID-19 pandemic, in addition to the speed at which the scientific community has responded, is multidisciplinary collaboration. A good example of this is the Global Health Interdisciplinary Platform (PTI), launched by the Spanish National Research Council (CSIC). This initiative seeks to combine all the capabilities of the largest research institution in Spain under one common objective: fighting the coronavirus.

The PTI, coordinated by Dr. Margarita del Val (CBMSO, CSIC-UAM), seeks to bring together all possible perspectives in order to achieve a global perspective of the COVID-19 pandemic. The main objectives of the platform are the identification of the origin and molecular mechanisms of the virus, the development of diagnostic and prevention methods, and the search for treatments (both vaccines and antiviral agents), without neglecting the dissemination of the relevant knowledge to the public. The multidisciplinary nature of the CSIC is crucial in tackling these challenges from multiple angles: biotechnology, nanotechnology, mathematics, data science, artificial intelligence, demography, sociology, philosophy, etc.

Around 250 research groups are already collaborating under the umbrella of the PTI, working against the clock to find short- and medium-term solutions without losing sight of their long-term goal. This coordinated effort will also lay the foundations for efforts to tackle future pandemics and other global health problems.

The PTI is structured into different thematic areas: PREVENTION, which focuses on investigating the variables, mechanisms, and action guidelines involved in fighting highly infectious agents, as well as establishing strategies to deal with the emergence and re-emergence of infectious diseases; TREATMENT, which encompasses projects aimed at identifying drugs, whether new or already approved (via a process known as drug repurposing), to treat COVID-19 or prevent it through vaccination; DISEASE, which seeks to thoroughly understand how the virus works, the body's response to it, and the actions required to contain it; IMPACT, which studies the effects of the incidence of the disease on society from scientific, political, economic, environmental, and social perspectives; CONTAINMENT, which covers efforts to reduce the incidence of SARS-CoV-2 through early detection and minimization or eradication of transmission via direct and indirect contact; and DISSEMINATION, which aims to provide society with proven information acquired through quality scientific research to avoid the dangers posed by hoaxes, disinformation, and infodemics. Transversally, advice will be sought on the protection of intellectual property when the time comes to patent discoveries or devices that may be worth protecting, developing, producing, and marketing. Other transversal activities will include the sharing of published material and information and the use of artificial intelligence for data processing.

Three researchers at the CIB Margarita Salas will coordinate sub-themes within these areas. In the TREATMENT working group, José María Sánchez-Puelles, co-head of the Energy Metabolism and Drug Development group, will coordinate drug repurposing, and María Montoya, principal investigator in the Viral Immunology group, will coordinate the inflammation sub-theme. Ángel Corbí, who heads the Myeloid Cell Biology group, will manage the immune response sub-theme within the DISEASE area.

The CIB Margarita Salas already has eight active projects within this platform, some in collaboration with other centres, led by Ignacio Casal, Sonsoles Martín-Santamaría, Eduardo Rial, Vicente Larraga, María Montoya, Fernando Díaz, Mercedes Jiménez, and Carmen Gil, Ana Martínez and Nuria E. Campillo, who co-direct the same project. Furthermore, several other researchers at the CIB Margarita Salas have made their knowledge and infrastructure available to the platform. This list, to which more names are added daily, includes Luisa Botella, Faustino Mollinedo, Cristina Vega, Dolores Pérez-Sala, and Javier Cañada. The PTI Global Health has shown that with a little effort, a structure can be rapidly put in place in which collaboration serves as the underlying key to a fight that involves us all. It should be noted that this platform will continue to operate once the COVID-19 health emergency has been resolved in order to use the experience gained to tackle future global health issues.

The following interview with Dr. Margarita del Val (CBMSO/CSIC-UAM), coordinator of the PTI Global Health, serves as a fitting bookend to this section.

How did the idea of creating this platform come about? Can you describe the response to this initiative, both at institutional level and the individual research groups?

In 2018, the CSIC began to create platforms to reorient different research groups within the CSIC to face a common challenge, with a very clear objective. Around 35 platforms had already been established and when the coronavirus pandemic emerged, the idea of creating this global health platform arose within the CSIC, which began to assess the level of interest among individual CSIC research groups. These groups, especially those with previous experience dealing with the issues that arise in the context of a viral pandemic, formed the basis of the platform and the coordinating committee. The coordinating committee includes three representatives of the CSIC's central organization who are truly fantastic and highly supportive, and are the real heart of the platform. In addition, other staff from the CSIC's central organization provide additional support, taking charge of all kinds of tasks including bibliography, communication, webinars, patent support, and intellectual property, to name a few.

The thematic areas and the projects in development cover a broad spectrum, but is it broad enough? Could there be any aspects that have not yet been contemplated?

The areas that are being addressed by the Global Health platform cover a wide spectrum, of course. There are about 250 groups interested in carrying out projects, but so far only 60 have been financed. This is limited in part by the availability of funding, the majority of which comes from donations by private companies or individuals. Funding from the Ministry of Science was also allocated to the coronavirus group at the CNB, led by Isabel Sola and Luis Enjuanes, and was received as early as January. Are there aspects that have not been contemplated? Well, as is logical in a basic research organization, we perhaps lack the necessary lines of communication with clinicians when it comes to bringing potential antivirals to clinical trials in order to first study the safety and subsequently dosage and efficacy. This is one area in which we are lacking: we do not have experts in that field within the CSIC. Perhaps we also lack the necessary expertise in economics to assess the pandemic's impact on society. But we have expertise in mathematics, chemistry, physics, all possible bio-related fields, nanotechnology, sociology, demography, mathematical modelling, pandemic modelling, we have engineers, experts in artificial intelligence ... we really have resources in all fields, apart from the shortcomings mentioned earlier.

What are the criteria for the distribution of resources within the platform?

Projects are evaluated and those that are the most viable, best suited to our needs, and led by the groups with the most experience are the ones that are financed first with the limited resources we have.

What should the public know about this commitment of the CSIC?

They should know that this commitment has redirected the research of many groups. It has allowed us to take advantage of the training acquired over many years by these researchers, who all this time have been conducting their research and making discoveries, contributing to basic knowledge in their respective fields and applying this knowledge by filing patents. And now, with the knowledge gained over the years by these groups, the researchers can provide added value by reorienting themselves to tackle as grave an emergency as one can imagine: a global pandemic. The advantage of the CSIC is its multidisciplinary nature. For this reason, the platform has been able to encompass multiple areas.

Are scientific criteria being taken into account when managing the de-escalation?

Some scientific criteria are being taken into account, as well as health criteria. De-escalation will depend on the availability of doctors, who will return to hospitals and primary care centers once they have recovered from infection. Another important reason for de-escalation is that it is essential to enable revival of the economy and society. Regarding scientific criteria, one clear example is social distancing, given that the virus is better transmitted at short distances. Another is the use of masks, which partially limit transmission of the disease by asymptom-

atic individuals, thereby reducing contagion. Another scenario in which scientific insights may be taken into account is the use of artificial intelligence-based contact tracing applications, which are being developed with a view to immediately identifying potentially infected individuals.

One of the priorities is the search for the vaccine. What kind of timeline can we realistically expect? What are the risks of rushing this process?

Yes, the search for a vaccine is a key priority, since a vaccine represents the ideal solution. Once developed, we could vaccinate a significant proportion of the population, at least 60–70% of them and especially at-risk groups, to generate a much safer environment. It is the best solution of all. It is also one of our priorities given the CSIC's particular strengths in this field. We have very good vaccine development projects, which constitute a key strength of the platform.

We have three vaccine projects currently ongoing. The first is the work of the coronavirus group of the CNB (Luis Enjuanes and Isabel Sola). They are working with RNA replicons from an attenuated virus that could induce a very complete immune response, since it contains a near-entire form of the virus, albeit without the capacity to multiply, making it very safe. The second project, headed by Juan García Arriaza and Mariano Esteban, also emerged from the CNB. This is based on the use of a very well-studied and effective vaccine vector, the same one used to develop the vaccine that helped eradicate smallpox. The third vaccine candidate, which forms the basis of a more recent project, is based on a DNA plasmid developed by Vicente Larraga at the CIB Margarita Salas. The advantage of this vaccine is that its production at an industrial level has already been demonstrated: a similar vaccine against leishmaniasis in dogs has already been tested and is about to be marketed.

What is a realistic timeline? I don't think it will be possible to have a Spanish vaccine ready before 2021, but it should be borne in mind that several vaccines will likely emerge worldwide, and several will be necessary. As soon as it has been shown to be effective, a vaccine would first be given to at-risk groups such as healthcare workers and the elderly, even if the duration of effectiveness is unknown and it remains unclear whether there are any long-term adverse effects of very low frequency. But all this will depend on how things evolve over time. Therefore, in these special circumstances in which not one but several vaccines will likely be used worldwide, it is very important that Spain actively pursues this avenue, as we have good vaccine candidates and have the capacity to develop them. This is why it is essential to invest a lot, not only in the research phase but also the intellectual property phase, and to have an industrial infrastructure capable of manufacturing these products in large quantities to obtain sufficient doses. With every month delay there will be hundreds of thousands of newly infected or dead. This is why everyone is racing to develop a vaccine, and when the first one is developed, even if it's not the definitive vaccine, it will be rolled out wherever possible. Meanwhile in other parts of the world other vaccines will be developed.

How can the knowledge gained during this pandemic help us to anticipate future pandemics? How will the platform contribute to this?

This global health platform will allow us to get closer to preparing everything necessary to confront a global health crisis. Right now, we are facing a viral pandemic, but this is not the only global health threat we face. We need to develop a much stronger research infrastructure, encompassing all areas of knowledge. Moreover, we must promote a more technological industrial infrastructure than that which currently exists in Spain. For example, in terms of the current pandemic, we should have had sufficient diagnostic kits from the beginning, or rapid tests, such as antibody detection tests, ready to roll out. Having these products produced within our own borders is also very important. Other examples are facilities capable of producing research-based vaccines or antivirals. Future challenges are only around the corner. The first challenge is a possible second or third wave of this pandemic, and we will have to react much faster and much better. We will also face other, already known challenges, such as antibiotic resistance, which implies an absence of any treatment for patients infected with a multi-drug resistant bacteria, against which there are no effective antibiotics. This is a real problem that has not yet reached catastrophic dimensions, but should be tackled before this happens. Early intervention is very important. And there are other examples. Climate change is posing global health challenges. Some tropi-

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cal diseases (such as dengue) are already present in the Mediterranean basin, and others are likely to follow as warmer temperatures attract the vectors that transmit them, such as mosquitoes and ticks. These tropical diseases that are coming our way are very difficult to cure. A third type of challenge, which we know less, but against which this platform must help us prepare, are pandemics caused by infectious agents, particularly viruses. One example is avian influenza, which we have been expecting for some time. Southeast Asia experiences very serious outbreaks every few years of new avian influenza strains with a lethality of 30–50%, and they manage to contain them because they are well prepared, and so far these outbreaks have not involved mutations that allow them to spread between people. So, we have been lucky, but luck can run out. We have to be prepared for another viral pandemic at any time. We can't know when, but one is likely to occur in the next decade. It could even occur before we manage to control the current global pandemic. We must be fully prepared.

Research at the CIB Margarita Salas to tackle the COVID-19 crisis

María del Carmen Fernández Alonso
PhD in Chemistry at the CIB Margarita Salas

On December 31, 2019, several cases of atypical pneumonia of unknown origin are reported in the city of Wuhan, in central China. Most of these infections appear to be related to a fish and seafood market where live animals are sold, which is then closed on January 1. On January 9, 2020, the Chinese authorities confirm the presence of an unknown coronavirus in 15 of the 59 cases of pneumonia detected so far. There are still no fatal cases, and transmission between humans appears not to occur. On January 10, with unprecedented speed, the full genome sequence of the virus causing the Wuhan pneumonia outbreak is released. The next day, phylogenetic analyses link the virus to group 2B of the genus Coronavirus, the same family as the coronavirus that causes SARS. The first death is reported on January 12; a 61-year-old man with chronic liver disease who frequented the Wuhan market. A day later, on January 13, the RT-qPCR protocol to detect this new virus, which is called SARS-CoV-2, is made available. On January 17 the viral genome sequence is added to GeneBank.

This timeline of the initial stages of the history of this new coronavirus provides an idea of the unprecedented speed at which the scientific community mobilized in the fight against SARS-CoV-2 and the search for effective treatments for COVID-19, the disease caused by this virus. At the same rapid rate at which the virus spread across the planet, scientists have made all their resources and tools available for research purposes: What is SARS-CoV-2? How does it attack the organism? What means do we have to identify it? And to combat it?

In this context, as already described in this issue of the newsletter, the Spanish National Research Council (CSIC) has established the Global Health Interdisciplinary Platform (PTI) , which initially will be oriented towards the study of the COVID-19 pandemic using an interdisciplinary approach that addresses all potential angles of this pandemic. Various groups of the CIB Margarita Salas are part of this platform. Numerous initiatives have been launched by the center to tackle the crisis unleashed by this pandemic. Some have already been mentioned in the editorial of this issue. Here, we will focus on the research projects that are already underway as part of the PTI Global Health.

From what we know so far, the virus is spread through the secretions of infected individuals, mainly by direct contact with respiratory drops of more than 5 microns (which can be transmitted distances of up to 2 metres), and by touching the mouth, nose or eyes with hands or fomites that have been contaminated with these secretions. The virus enters the cell via the angiotensin-converting enzyme 2 (ACE-2) receptor, which is mainly present in the kidney, lungs, and heart. ACE-2 has been linked to protection against hypertension, arteriosclerosis, and other vascular and pulmonary processes. In the case of this virus, ACE-2 recognizes the S (spike) protein expressed on the viral surface. The clinical signs of COVID-19 are varied, being the main high fever, dry cough, and respiratory problems. In severe cases, the presence of elevated levels of interleukin-6 and other proinflammatory cytokines has been observed, indicating that these patients develop a syndrome known as "cytokine storm". This occurs in response to activation of large numbers of leukocytes (neutrophils, macrophages, and mast cells) and the release of large amounts of proinflammatory cytokines.

Inflammatory mechanisms in SARS-CoV-2 infection

The pathophysiology of SARS-CoV-2 remains unclear. In particular, it is unknown why certain people respond to infection with excessive inflammation, which can lead to a severe infection and even death. The INFLA-COVID project, proposed by Dr. Maria Montoya of the Viral Immunology group, focuses specifically on identifying these inflammatory mechanisms.

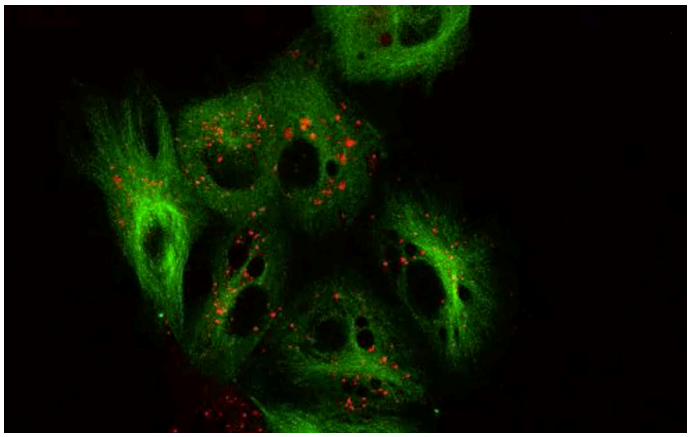
In a first phase of the project, a platform will be generated to identify the viral determinants that modulate inflammation and/or cell death. In a second phase, the tools developed and knowledge gained in the first phase will be applied to develop new strategies to control inflammation that could ultimately serve to treat seriously ill patients. Detailed information on the interaction between SARS-CoV-2 and the host immune system will help unravel the mechanisms driving persistent pulmonary inflammation and to identify possible means of reducing the risk of excessive inflammation caused by the virus. In carrying out this project, Dr. Montoya's group will collaborate with the University of Córdoba, the National Cnter for Cardiovascular Research (CNIC), and the López Neyra Institute of Parasitology and Biomedicine in Granada.

Disruption of viral microtubule-mediated transport processes

Microtubules are essential components of the cytoskeleton that are crucial in intracellular trafficking and represent one of the most widely used routes of virion entry and/or exit in multiple infectious processes. Beta-coronaviruses are no exception, and depend on microtubules for cellular internalization and subsequent release. In the specific case of SARS-CoV-2, high blood levels of cytokines are associated with worsening of the disease due to feedback-mediated hyperactivation of the immune system that in turn triggers the "cytokine storm". Intracellular trafficking of cytokines and their correct localization in the immune synapse is also dependent on microtubules.

Modulation of microtubules could prove an as-yet unexplored bivalent approach to the treatment of viral infections, in particular those that cause Severe Acute Respiratory Syndrome (SARS). Taking into account the wide range of viral processes in which the cytoskeleton, and in particular microtubules, are actively involved, a drug targeting these components could simultaneously slow down viral activity and prevent exacerbated cytokine release.

The project coordinated by the Microtubule Stabilizing Agents group, led by Dr. Fernando Díaz, focuses on evaluating the effect and dose-response of agents used in clinical practice to target microtubules and inhibit viral replication in A549 cells of lung tumours.



Tool to evaluate compounds (F. Díaz laboratory): movement of the viral peptide (red) via microtubules (green)

The group's objective is to assess the therapeutic viability of these agents in COVID-19 patients with poor prognosis. In collaboration with Dr. Covadonga Alonso (INIA), exhaustive screening will be carried out to identify compounds that efficiently inhibit viral replication and to determine the concentration at which this inhibition occurs. The aim is to block the transport of viral proteins and cytokines via the cytoskeleton. The Biosensors and Chemical Biology group of the CIB Margarita Salas, led by Dr. Valle Palomo, is also participating in the project, and seeks to design and synthesize different peptide sequences that mediate binding to molecular transporters that travel along microtubules. These peptides will be conjugated with different fluorophores, including Quantum Dots luminescent nanoparticles, in order to visualize the intracellular transport in which microtubules participate

Investigation of the interaction between SARS-CoV-2 and the host at the proteomic level.

There are many other aspects of the interaction between SARS-CoV-2 and its host that still remain to be deciphered. To better understand these processes, Dr. Ignacio Casal is participating in a project, coordinated by Dr. Fernando Corrales (CNB), that will study this interaction at the proteomic level.

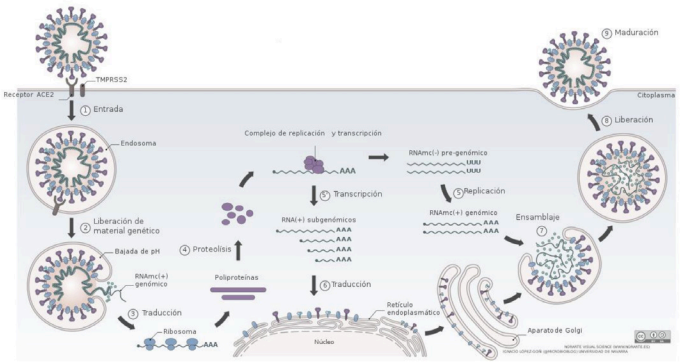
This project brings together the 22 laboratories of the ProteoRed-ISCIII network, which will tackle the following objectives using a coordinated approach: (1) study the immunological response of COVID-19 patients in order to identify viral epitopes and antibody profiles that

allow the development of vaccination and stratification strategies, and the identification of protected individuals; (2) characterize the serum proteome of patients to develop prognostic and monitoring methods; (3) establish a quality-control platform for peptide products that will be synthesized in this and other related projects; and (4) characterize the interaction of the viral proteome with the infected cell. These objectives will facilitate the development of new diagnostic, therapeutic, and vaccination strategies necessary to control current and future pandemics.

Integrins are used by many human viruses as molecular receptors, and in the case of SARS-CoV-2 have been proposed to act as alternative co-receptors to ACE-2, and to possibly participate in disease transmission and pathology. RGD sites (consisting of an Arg-Gly-Asp tripeptide) are structural motifs that mediate binding to integrins, and are present in many proteins. The S protein of this new coronavirus acquired a RGD motif that was absent in other members of this virus family. The Mechanisms of Cancer Metastasis group, led by Dr. Casal, will focus on studying the RGD motif present in the S protein of SARS-CoV-2, and will investigate the possibility of blocking the motif using antibodies, thereby preventing the virus–integrin binding. The RGD motif could thus constitute an interesting alternative therapeutic target to the ACE-2 receptor. Antibodies have already been developed against the RGD motif found in human cadherin 17 (CDH17) protein. This project will examine their potential utility in blocking the RGD site in SARS-CoV-2.

Blocking the entry of SARS-CoV-2 using antivirals and ACE-2 fragments as bait

The identification of inhibitors, in this case targeting SARS-CoV-2 binding to the ACE-2 receptor, is the objective of the multidisciplinary project coordinated by Dr. Sonsoles Martín Santamaría together with María Jesús Pérez (IQM-CSIC). Blocking viral entry into cells is a key step in breaking the viral replication cycle. This collaborative project, which also involves researchers from other CSIC centres including the IBV, IQM, and I2SysBio, addresses this challenge from a multidisciplinary perspective, using atomic and molecular approaches to ensure complete biological evaluation of the virus. The project combines the experimental and computational searching of libraries to identify novel compounds that inhibit virus entry; the design of peptide inhibitors derived from ACE-2 by means of directed mutagenesis; and the design and synthesis of modified compounds to improve binding properties. This strategy will generate small molecules and therapeutic proteins that could be potential candidates for the prevention or treatment of COVID-19.



Replication of SARS-CoV-2 within cells. Vega Asensio (Norarte) and Ignacio López-Goñi (UNAV)

As part of this project, the Computational Biological Chemistry group, led by Dr. Sonsoles Martín Santamaría, will carry out computational studies to generate a model of the interaction between the SARS-CoV-2 S protein and the ACE-2 receptor, thereby enabling the design of inhibitors and virtual screening against generic drug databases (drug repurposing) and other commercial and in-house repositories.

Metabolic reprogramming of the host in viral infection

When a virus infects an organism, it hijacks the cellular metabolism of infected cells to provide itself with energy and precursors to sustain synthesis of the macromolecules necessary to generate new viral particles. The resulting metabolic change in the infected cell resembles that which occurs in tumour cells. In the case of coronaviruses, the specific effect of the virus on the energy metabolism of host cells remains unknown.

The project led by researcher Eduardo Rial, from the Energy Metabolism and Drug Development group, will study host metabolic reprogramming induced by the SARS-CoV-2 virus. Elucidation of the molecular mechanisms underlying this process would further our understanding of the evolution of the infection, and allow evaluation of the efficacy of specific drugs that can reverse the reprogramming of cellular metabolism. Such compounds would constitute potential antiviral agents, and could lead to drug repurposing for clinical use.

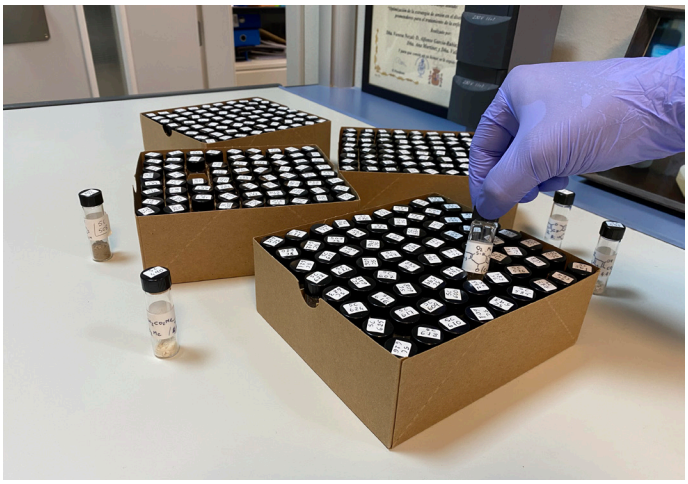
Drug repurposing

Several projects proposed by the CIB Margarita Salas seek to identify medications effective in the treatment of

COVID-19 patients though drug repurposing.

The Translational Medicinal and Biological Chemistry group led by Drs. Ana Martínez, Carmen Gil, and Nuria Campillo, is working to identify drugs that are currently in commercial use or in clinical development and could be immediately tested in phase II/III clinical trials. Candidate drugs for repurposing to treat COVID-19 are being identified from libraries of compounds approved by the FDA or EMA and by virtual screening using different chemoinformatic strategies.

The possible repurposing of GSK-3 inhibitors for the treatment of COVID-19 will also be studied. This family of compounds had already shown antiviral activity in previous coronavirus infections. Because tideglusib, a non-competitive GSK-3 inhibitor designed by this group, is in advanced stages of clinical development, its efficacy against SARS-CoV-2 is currently being evaluated in collaboration with the antiviral screening group



Part of the compound library of the group of Ana Martínez, Carmen Gil, and Nuria Campillo

led by Pablo Gastaminza in the National Center for Biotechnology (CNB). Initial results are encouraging, and final studies are pending before an *ad hoc* clinical trial can be designed.

In parallel to repurposing strategies, another approach to rapidly identify potential treatments is to screen for compounds similar to the drugs currently used to treat COVID-19 patients (similarity-based virtual screening). Other proposed research avenues include the identification of alternative pharmacological targets to prevent virus entry into the host based on knowledge generated in ongoing projects, as well as proteomic studies of the virus's S glycoprotein. Initial studies have enabled the selection of over 100 compounds targeting nine distinct targets. These compounds are already being evaluated at the CNB. Success of this proposed strategy could have an enormous social impact, and could identify treatments that could be administered to patients affected by the current pandemic.

Donation of compound libraries for pharmacological evaluation against SARS-CoV-2

The Microtubule Stabilizing Agents group at the CIB Margarita Salas, led by Dr. Fernando Díaz, has one of the world's largest libraries of microtubule-modulating compounds, containing all microtubule-modulating drugs in clinical use and a large number that are currently under study. This library of compounds has been donated to the CNB, specifically to Pablo Gastaminza's group, to be evaluated in the search for compounds that efficiently inhibit viral replication.

The Energy Metabolism and Drug Development group, co-directed by Dr. José María Sánchéz-Puelles, has also donated the Prestwick commercial compound library to the CNB for evaluation. This library contains more than 1000 out-of-patent drugs of wide chemical and pharmacological diversity addressed to over 400 therapeutic targets with demonstrated bioavailability and safety in humans.

Development of a recombinant DNA-based vaccine

In addition to strategies aimed at discovering a new drug or repurposing one already known to alleviate the effects of SARS-CoV-2 infection, the CIB Margarita Salas will also launch a project to search for a vaccine that prevents contagion by the virus.

The Molecular Parasitology Group led by Vicente Larraga, Research Professor *ad honorem*, aims to use a novel recombinant DNA vaccine that introduces the gene of an antigen of a parasite to induce protection against it, instead of an attenuated form (or a fragment) of the parasite or a purified protein.

This group has previous experience in this field, since they have developed a vaccine with these characteristics that protects against canine leishmaniasis and is already in Phase IV (awaiting a permit from the European Medicines Agency for manufacturing and marketing). The vehicle for this vaccine is a synthetic DNA plasmid (pPAL), developed in the laboratory of Prof. Larraga, that allows integration of the selected parasite antigen into the genetic material of the cells of the recipient mammal. These cells will then produce the antigen, which will be recognized by the immune system of the vaccinated animal and will induce protection when natural infection occurs. An added advantage of this vehicle is that it does not require the inclusion of adjuvants in the vaccine.

This same procedure can be applied to the SARS-CoV-2 virus, since the vehicle has been designed for mammals, including humans, and is therefore free of

any potentially toxic sequences. In the case of SARS-CoV-2, potential protective vaccine antigens include (1) the S protein expressed on the viral surface; (2) its S1 and S2 subunits; and (3) the fragment that binds to the ACE-2 receptor, via which SARS-CoV-2 penetrates the membrane of the target cell.

Currently, the corresponding DNA molecules to be introduced into the previously developed vehicle are being synthesized. Their safety and efficacy against viral infection will then be tested in a mouse model (e.g. in animals transfected with the human ACE-2 receptor). Alternatively, if available, macaques could be used. Positive results would pave the way to phases I and II of human testing. An additional advantage of the development of this vaccine is that the industrial scaling process of the vaccine candidate has already been carried out. This would significantly accelerate the industrial phase of manufacturing, human testing, and subsequent production.

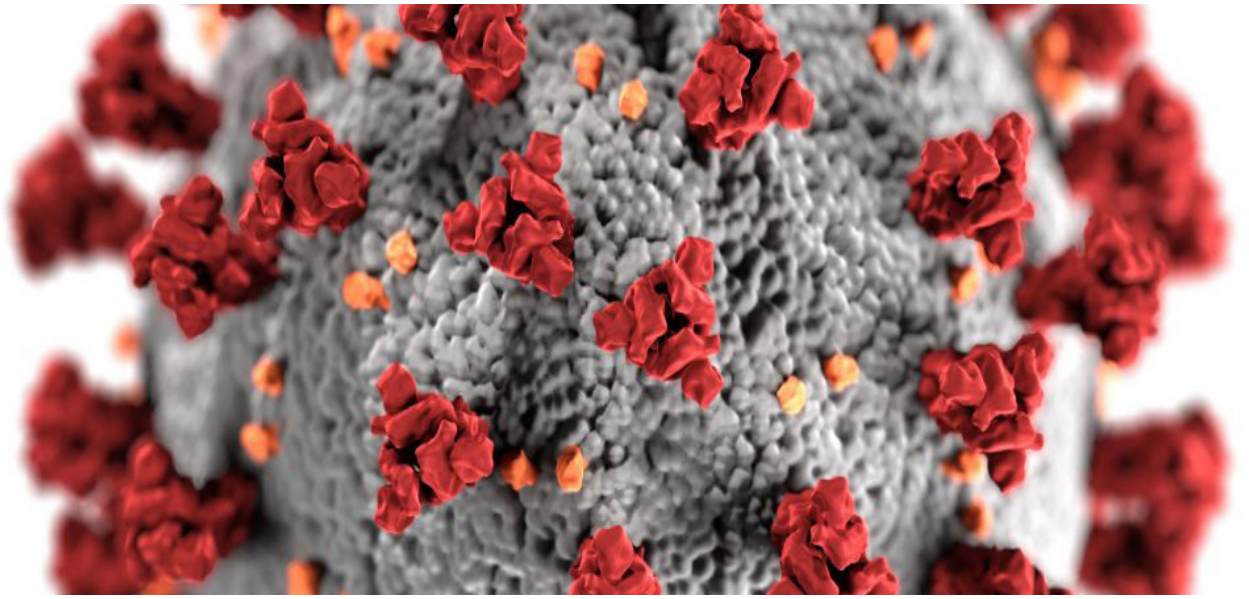
Scientific, philosophical, and social analysis of COVID-19: social repercussions, ethical implications, and the culture of pandemic prevention

A comprehensive approach to the study of a pandemic also entails addressing the social impact, ethical aspects, and the culture of pandemic prevention. This is the objective of the project led by Matilde Canelles (IFS) within the PTI Global Health, in which the participation of the CIB Margarita Salas is coordinated by Drs. Mercedes Jiménez and Nuria E. Campillo.

This multidisciplinary project aims to achieve several complementary objectives in the short, medium, and long term, from different perspectives. One strand will examine the social impact of COVID-19 and the ethical dilemmas associated with this unprecedented situation that can negatively impact coexistence. This will be achieved through the processing of bibliographic data, statistics, interviews, big data, etc. A second strand of the project will study the adoption of measures against pandemics that promote co-responsibility among citizens, the dissemination of measures aimed at strengthening a culture of prevention and changing behaviours, and the inevitable repercussions of the social changes that are taking place.

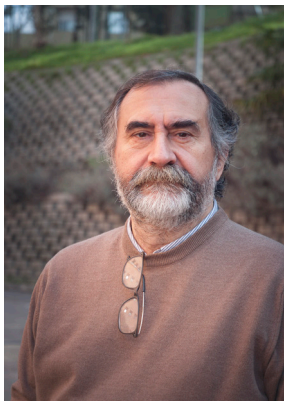
The contribution of Dr. Jiménez and Dr. Campillo focuses on the design, development, and implementation of public health information measures and tools to effectively respond to the epidemic by generating a broad range of material (e.g. audiovisual material) about pandemics, health alerts, and preventive measures, by examining the effects on different sectors of the population, and by studying the efficient dissemination of this material throughout the population via mass media, social networks, associations, leisure centers, and educational institutions, among others.

In December 2019, the world learned of the arrival of a new virus of animal origin, with the ability to infect humans, spread very efficiently between them, and cause serious health problems. Immediately, the scientific community mobilized to seek answers to the questions that arose and thereby tackle the pandemic. At the CIB Margarita Salas, as described above, various lines of research have been adapted to fight this health emergency based on experience acquired over decades of work. This way, based on knowledge accumulated in a rigorous and systematic manner, we can address not only the current pandemic but also health and environmental challenges that may arise in the future.



COVID-19 and the immune response

Ángel Corbí
CSIC Research Professor at the CIB Margarita Salas
Coordinator of the "Immune Response" sub-theme within the "Disease" working group of the PTI Global Health



The SARS-CoV-2 epidemic has forced society to adapt quickly to the new public health panorama. One of the ways in which the CSIC has responded to this challenge has been to launch the Global Health Interdisciplinary Platform (PTI), the aim of which is to mobilize CSIC research groups to address the problem of COVID-19 from multiple perspectives: prevention, containment, treatment, and information dissemination. Within the structure of the PTI Global Health, the DISEASE group, coordinated by Antonio Alcamí and Iñaki Comas, addresses aspects directly related to the pathogen (structure and genetics of the virus) and the response to it (severity of infection and immune response), through the promotion and coordination of projects proposed by researchers from the CSIC and focused on these specific aspects.

Given that COVID-19 is an infectious disease, the immune and inflammatory responses to SARS-CoV-2 are of great scientific importance and social interest: study of these processes should help unravel the mechanisms underlying the pathology, and identify key points of intervention for both treatment and prevention. In the few months since the start of the epidemic, numerous articles and comments have been published on how the immune system, and especially the cells of the innate immune system (macrophages, neutrophils), act in the early stages of infection, playing critical roles in the inflammatory pulmonary response and in the development of the "hyperinflammatory" and profibrotic response that triggers pathological systemic alterations (liver and kidney damage, heart failure) in patients with poor clinical course. In fact, recent studies have identified the lung macrophages responsible for the fibrotic response, and biomarkers of severity that are linked to macrophage activation and the coagulation process. Unfortunately, despite these significant advances, there remains some confusion about certain key aspects of the pathology and treatment of this disease. This confusion is partly due to the dissemination of insufficiently verified data and a lack of rigour in some scientific studies and clinical trials that have already been made public ("Infodemia").

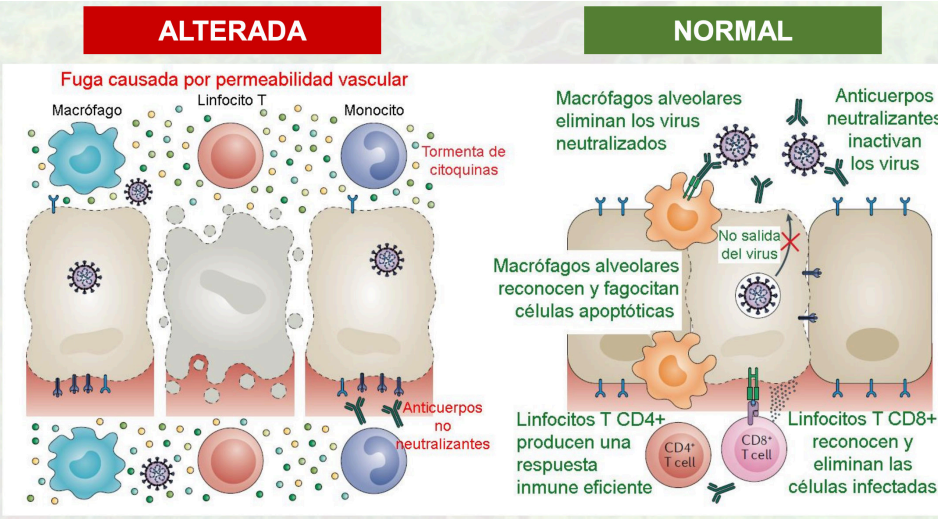
Control of the hyperinflammatory and profibrotic response that occurs in SARS-CoV-2 patients with a poorer clinical course is the ultimate objective of many therapeutic strategies and clinical trials currently underway. Anti-interleukin-6 (IL-6)/IL-6R antibodies, which are used in the treatment of rheumatic diseases, appear to be effective in controlling this response. This discovery underscores how knowledge generated in one specific field can end up facilitating the treatment of other, apparently unrelated pathologies. This should be borne in mind when prioritizing lines of research in any field, since responses to clinical and social problems are often based on work done in apparently unrelated areas of research. Who would have guessed that the characterization of high levels of interferon in bats ("what is the purpose of measuring IFN in bats?") would help explain the severity of infections caused by viruses originating from these animals?

Regarding the immune response, studies of the mechanisms underlying the response to SARS-CoV-2 are essential to develop and optimize vaccines that are effective against COVID-19. According to the WHO, there is still no evidence to indicate that long-term protective immunity is generated against SARS-CoV-2. This issue must be resolved as soon as possible to aid development and generation of effective vaccines. The PTI Global Health has recognized the urgency of this issue, and is already financing groups working directly in this area.

Right now, there is an urgent need to strongly support research groups with solid research backgrounds in the study of coronavirus infections. It should be noted that much of the severe pathological alterations observed in COVID-19 patients have been previously described for SARS-CoV, including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). These previous studies have thus proved helpful in unravelling the pathology of COVID-19. However, it should be emphasized that once the immediate socio-health crisis has passed this support must be extended to research groups that can contribute relevant knowledge when confronting threats to public health, based on knowledge gained

in their respective fields of expertise.

Finally, it is also an opportune moment to call for the integration of CSIC research groups working in the field of biomedicine into the Institutes of Health Research (IIS) of the Institute of Health Carlos III (ISCIII). Although demanded by many groups within the CSIC for almost 10 years, this change has been impeded by various administrative sectors. In my opinion, the incorporation of the CSIC researchers under the umbrella of the IIS would have allowed a more effective response by these researchers to the current health crisis, as well as better coordination of the healthcare tasks and clinical trials promoted by the National Health System (SNS). Looking to the future, and to one of the ultimate long-term objectives of the PTI Global Health, which is "*Defining a path of action [...] to ensure [...] the availability of vaccines, effective antivirals, rapid and early diagnostic methods applicable to healthcare, epidemiological surveillance protocols, and primary care and hospital resources that, to the extent possible, help avoid collapse of the health system, ensure epidemiological control, and avoid negative impacts on public health*", integration of CSIC research groups into the ISCIII Health Research Institutes could help ensure that these objectives are achieved.



Altered immune response vs. normal immune response (SEV)

* *The opinions expressed in this text reflect the author's point of view and not necessarily that of the CIB Margarita Salas.*

Control inflammation in the context of COVID-19 treatment

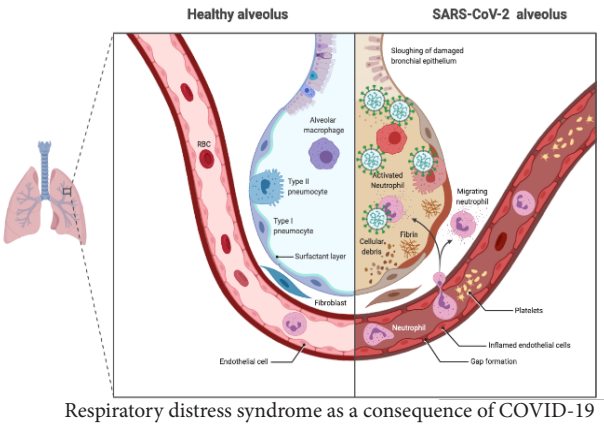
María Montoya
Scientist at the CIB Margarita Salas
Coordinator of the "Control of inflammation" sub-theme within the "Treatment" working group of the PTI Global Health

The Global Health Interdisciplinary Platform (PTI) mobilizes around 250 research groups from different CSIC centers in collaboration with other institutions, public administration, and companies. The PTI was conceived to provide an interdisciplinary approach to the pandemic caused by the SARS-CoV-2 virus. As such, it is structured into seven major areas (origin, prevention, disease, containment, treatment, impact, and dissemination). The objective of the vaccination and treatment area, coordinated by José María Benlloch and Pilar Marco, is to identify compounds and vaccines effective against COVID-19, the disease caused by this virus. The work of this group is divided into 5 sub-themes: design of new antivirals, drug repurposing; production and evaluation of therapeutic antibodies (both for diagnostic purposes and as a possible means of curing the disease); vaccines; and inflammation control (using compounds that prevent the inflammatory reaction triggered by the virus, and alleviate or prevent the symptoms associated with the disease).

Infection with SARS-CoV-2 coronavirus has a mild course in approximately 80% of those infected. However, a small proportion of patients develop a serious condition that can ultimately be fatal. Based on studies carried out to date, it appears that pulmonary inflammation underlies this exacerbation, which can lead to death.

In general, inflammation is a response of the immune system designed to protect the body from infection and/

or injury. However, in some diseases excessive or uncontrolled inflammation can itself be the cause of pathology. Inflammation can involve the secretion of a series of soluble factors (cytokines) and the production of special immune cells (e.g. neutrophils, macrophages). An excessive inflammatory response can give rise to a "cytokine storm", caused by the secretion of high concentrations of inflammatory cytokines and resulting in tissue damage. In certain patients with SARS-CoV-2, excessive inflammation results in pulmonary tissue damage, which



Respiratory distress syndrome as a consequence of COVID-19

in turn triggers acute respiratory distress syndrome (ARDS). The severity of the clinical picture in critically ill patients is not solely due to viral replication, but also to their own immune response. ARDS is characterized by difficulty breathing and low blood oxygen levels, and can have a fatal outcome. Furthermore, the release of certain cytokines due to uncontrolled inflammation can cause multi-organ failure, affecting in particular the cardiovascular, liver, hepatic and renal systems.

The INFLAMMATION CONTROL sub-theme focuses on research projects that seek to identify the inflammatory mechanisms that influence disease severity and possible pathways via which these mechanisms could be modulated. The projects range from basic research to further our knowledge of the molecular basis of the inflammatory process triggered by SARS-CoV-2, to the search for compounds or drugs that can modulate this process and potentially be used to treat severely ill patients. Using novel strategies, these projects will tackle issues ranging from the processes involved in the inflammation cascade (e.g. the inflammasome or viral determinants that trigger inflammation) to the repurposing of compounds such as MAP kinase inhibitors, anti-parasitic molecules, and nanocomposite immunosuppressive agents.

Control of inflammation plays a central role in the pathology of many diseases, COVID-19 included. As such, discoveries arising from the projects in this sub-theme could have important future applications in other pathologies.

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Drug repurposing: old drugs with new therapeutic indications

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Coordinator of the "Repurposing" sub-theme within the "Treatment" working group of the PTI Global Health

Why drug repurposing?

For the past three decades, the predominant drug discovery strategy within the pharmaceutical industry has been to search for new chemical entities with particular pharmacological targets of interest. It is estimated that this classical approach to drug development has a failure rate of over 90%, which is a cause of great frustration for the researchers involved and entails huge economic losses for funding bodies. Despite a 2-fold increase in investment in pharmaceutical I + D during the first decade of this century, the number of treatments approved by the American Food and Drug Administration (FDA) remained constant[1].

Sir James W. Black, winner of the 1988 Nobel Prize in Medicine and Physiology, was the first to demand that the scientific community expand the spectrum of pharmacological research to include the search for new applications of already approved and marketed drugs, whether old or new.

This strategy has led to the emergence of drug repurposing as a new area of pharmacological research, defined as the reorientation of drugs for clinical use for new therapeutic indications[2]. By exploiting the long his-

tory of clinical use of certain drugs in humans (including available bioavailability data and a demonstrated safety profile), repurposing offers major advantages over other drug discovery strategies.

"The most fruitful basis for the discovery of a new drug is to start with an old drug," Sir. James W. Black

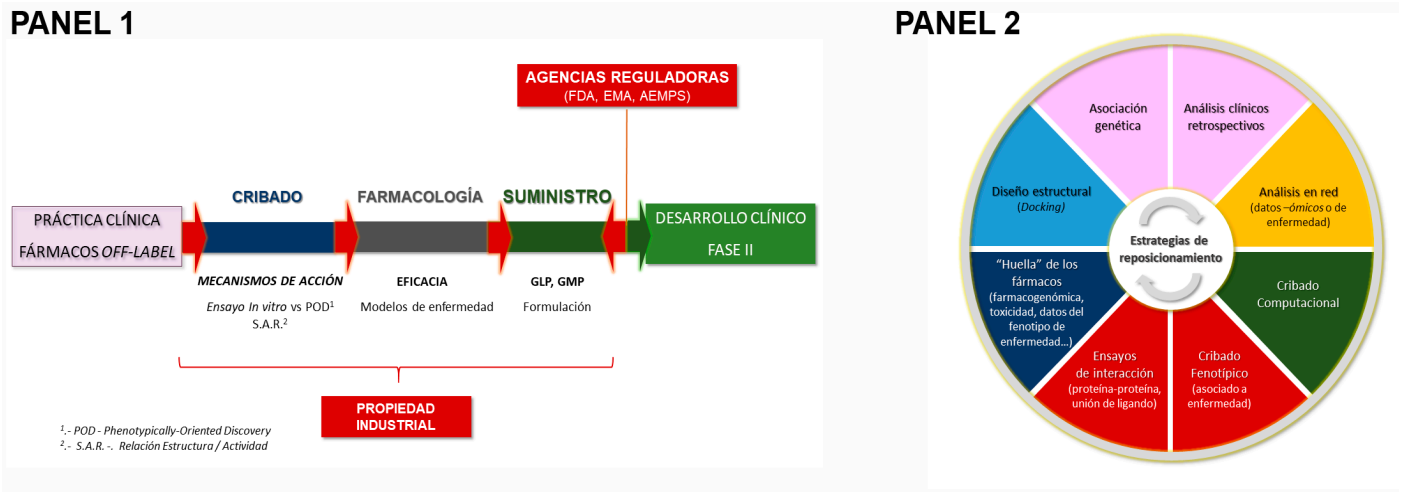
Drug repurposing strategies already accounted for approximately 30% of new FDA-approved drugs and vaccines in 2013. Once efficacy has been demonstrated for a new therapeutic indication, the drug developer can request authorization to regulatory agencies to move directly to clinical phases in order to study efficacy for the new indication. This entails significant savings of both time and money. Each drug in clinical use has about 20 different applications outside of the indication for which it was originally approved (off-label use). Two thirds of these off-label indications are initiated by the doctors responsible for prescribing the drugs. It is estimated that up to 75% of known drugs may have novel therapeutic applications[3].

The repurposing strategy has opened up the area of drug discovery to the academic world. Academic communities have greater freedom of action and greater flexibility of execution, thus guaranteeing persistence in high-risk activities that are often abandoned by pharmaceutical companies. Numerous commercial collections provide access to most drugs approved by regulatory agencies, including patent-free drugs. The protection of research findings is one of the weaknesses of drug repurposing: the classical patent based on a drug's chemical scaffold is no longer a valid approach. However, there are alternatives means to protect investment, including patents for use, dosing, combination, and joint diagnostic/therapeutic applications.

Repurposing as a therapeutic strategy in the context of health crises

Today, about a third of the world's population is under some form of lockdown as a public health measure to stem the spread of the SARS-CoV-2 coronavirus, the cause of COVID-19. The key to emerging from this overwhelming confinement is to increase testing in a representative portion of population (*test, test, test*) and implement contact tracing (*test, test, test*). The return to the workplace will depend on the immune status of both individuals and society at large, and a return to normality will depend on the availability of repositioned drugs[4] and, in the medium term, effective vaccines.

The existing clinical arsenal has been key to the initiation of dozens of SARS-CoV-2 clinical trials of repurposed drugs. Underscoring the extraordinary dedication of those involved in this field, in Spain alone 119 such clinical trials have been launched. Meanwhile, at the international level, more than 100 countries have joined the Solidarity project[5], a clinical mega-trial coordinated by the World Health Organization (WHO) that constitutes the largest repurposing effort in the history of medicine. The trial has recruited patients to be treated with four key drugs: remdesivir; chloroquine or hydroxychloroquine; lopinavir + ritonavir; and lopinavir + ritonavir combined with interferon beta 1a (LPV/RTV-IFN). Repurposing efforts are focused on virus replication and the inflammation process that arises during the second phase of the disease as a consequence of the so-called cytokine storm. The first promising candidate in the Solidarity trial was remdesivir (GS-5734), which has been currently in clinical trials for the treatment of



Drug repurposing: stages (panel 1) and strategies (panel 2). Figure adapted from Sudeep Pushpakom et al. (2019) Drug repurposing: progress, challenges and recommendations. Nature reviews - Drug discovery 41-58

Ebola virus infections and inhibits* the replication of SARS-CoV-2 in culture and in animal models[6]. On the other hand, the treatment of choice in hospitals, despite its side effects, has been hydroxychloroquine, the efficacy of which is been continually monitored and is the subject of some controversy regarding the rigour and flexibility of scientific journals in these troubled times[7].

In this context, institutions must promote the development of scientific policies for pharmacological research by designing robust platforms for urgent action based on drug repurposing strategies, which will allow us to face current and future pandemics and to direct therapeutic strategies against other diseases in cases of clinical emergencies affecting any area of human health.

** Update: European regulatory authorities finally approved on 25/06/2020 its use against the coronavirus SARS-CoV-2 (https://www.ema.europa.eu/en/news/first-covid-19-treatment-recommended-eu-authorisation)*

**[1] The opinions expressed in this text reflect the author's point of view and not necessarily that of the CIB Margarita Salas.*

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Knowledge is power

Mercedes Jiménez
CSIC Scientist at the CIB Margarita Salas

In just a few months a (non-computer) virus has invaded the entire world. At the same time, our homes, mobiles, and tablets have been invaded by information relating to this pandemic. The implications of both invasions for scientific communication and the dissemination of knowledge have been extraordinary.

Thanks to basic scientific research, we know that the extreme virulence of the virus is largely due to the fact that it is not recognized by our immune system. Proving lethal to the vulnerable, it has caused the confinement of billions of people worldwide and the paralysis of economic activity so that health systems can cope with treating the sick. Furthermore, globalization has played a key role in spreading the epidemic in record time.

We live in an information society and new communication technologies provide us with immediate knowledge of events occurring even in the remotest parts of the world.

Throughout the history of humanity, pandemics spread more rapidly than knowledge of the fact, which only served to further increase their terrible impact. A lack of knowledge about the origin, transmission, and treatment of diseases fuelled panic and led authorities and citizens to take irrational, dangerous, and inappropriate actions.

Today, fortunately, thanks to advances in science and communication, we have access to daily updates on data, statistics, curves, treatments, diagnoses, preventive measures, etc.

And while we await the development of an effective vaccine or treatment for the virus, our homes, which provide us with physical and moral protection against this invader, are invaded by all kinds of information disseminated both actively and passively by the press, radio, television, and social networks.

How can we assimilate so much data? While psychologists recommend avoiding compulsive consumption of information, the need to know what is happening means we are permanently connected to our sources of news. But are they reliable? Fear of the unknown can fuel the proliferation and spread of hoaxes and fake news. Panic is irrational and can manifest as an urgent need for information, without determining whether the source is

sufficiently credible.

The response of science, and scientists, can help provide context to this pandemic. The promotion of critical knowledge-based thinking is essential to confirm the credibility of information about our understanding of the disease; the variability of vulnerability; the day-to-day evolution of the pandemic; and the approaches that can be expected to contain it. How should we act, and why?

We are witnessing a continually changing reality and an uncomfortable level of uncertainty. Recommendations to citizens have been modified as the panorama has changed, from the appearance of the virus in a remote Chinese province to the presence of numerous cases in northern Italy, from the WHO's warning of a possible epidemic to total acceptance of a global pandemic. To wear a mask, or not? To isolate ourselves, or not?

Faced with a continually changing situation, correct and truthful information is key.

As scientists we know that science, knowledge, is not immutable. It changes as we delve into the mechanisms that govern natural laws. There are no dogmas or immutable truths. For this reason, among others, communicating science and scientific knowledge is far from easy.

But the case at hand is different. In the current climate, the general public are more favourably predisposed to the consumption of public health information. And this is what worries us the most. Perhaps that is why we have more or less readily accepted the strictest confinement measures ever imposed in the past 100 years.

In the current public health emergency, the increased appetite of the public for information to keep them abreast of current events presents two key opportunities for the dissemination and communication of science.

On the one hand, there is an opportunity to increase the public's knowledge of scientific topics that are otherwise considered too difficult to understand: for example, what is a virus, how does it reproduce, how does it cause the disease, and why is it claiming such high numbers of victims. Right now, the general public is better informed about this new virus than about the common flu.

Hand in hand with increased concern for public health, science and scientific knowledge is entering the households and mobile phones of all citizens. This brings a greater awareness of the importance of such knowledge, and increases public confidence in science and scientists to solve serious problems, in turn generating greater support for investment in science that will have an impact far beyond the field of public health alone.

The public now have answers to questions such as "What is the point of science?"

This increased confidence in science also helps to combat the phenomenon of fake news. Finding reliable sources or asking a scientist is now recognized as the best way to resolve curiosity or alleviate fear. Why pay attention to a *Youtuber*, a *WhatsApp*, or a *tweet* when I can get first-hand information from a specialist in the field?

Despite the uncertainty, discrepancies, and contradictory decisions, society is accepting that science is not immutable, that its strength is based on contrasting the findings of repeated experiments, and that this apparent contradiction is in fact the day-to-day reality of scientists.

Never has there been a more favourable context for the dissemination of scientific knowledge, without fear of rejection of complex concepts.

María Montoya on *Cuatro Al Día*, one example of the participation of our researchers in news coverage on the pandemic

We should seize this opportunity to increase society's scientific knowledge, and use that knowledge to generate and cultivate vital critical thinking skills. Hopefully, the virus of scientific curiosity is one that is here to stay.

Fighting the COVID-19 pandemic is also helpful in fighting ignorance. Valuing science and accepting scientific culture without fear is also a victory over the virus of fear and ignorance.

Scientific information has been at the forefront of public consciousness day by day during our confinement, and is now considered something natural and necessary, almost like the weather forecast.

** The opinions expressed in this text reflect the author's point of view and not necessarily that of the CIB Margarita Salas.*

**[1]Mercedes Jiménez coordinates, together with Nuria E. Campillo, the participation of the CIB Margarita Salas in the project "Scientific, philosophical, and social analysis of COVID-19: social repercussions, ethical implications, and the culture of pandemic prevention". This project is integrated within the PTI Global Health.*

A mission for the history books

Begoña García Sastre
Journalist (supported by a contract from the *Fondo de Garantía Juvenil*)

The scientific community is focusing all efforts on producing a vaccine against COVID-19, the disease caused by the SARS-CoV-2 virus that has led to a near unprecedented pandemic and resulting global paralysis.

In Spain, 10 such projects are currently underway. Three of these, led by researchers from the CSIC (one coordinated by Prof. Vicente Larraga at the CIB Margarita Salas), are well positioned to develop what would constitute the ultimate solution to the current crisis. Although similar projects in other countries are at more advanced stages, scientific efforts must continue nonetheless.

Generating a Spanish vaccine, and having the capacity to produce the necessary doses to first vaccinate health workers and at-risk groups, followed later by the rest of the population, would be a milestone in the history of Spanish research and medicine. This is not a simple objective, and Spain still lacks a strong technological-industrial infrastructure. However, the objective is not unattainable. The adaptation of veterinary vaccine laboratories and factories to enable production of a vaccine, once eventually developed, is currently being explored.

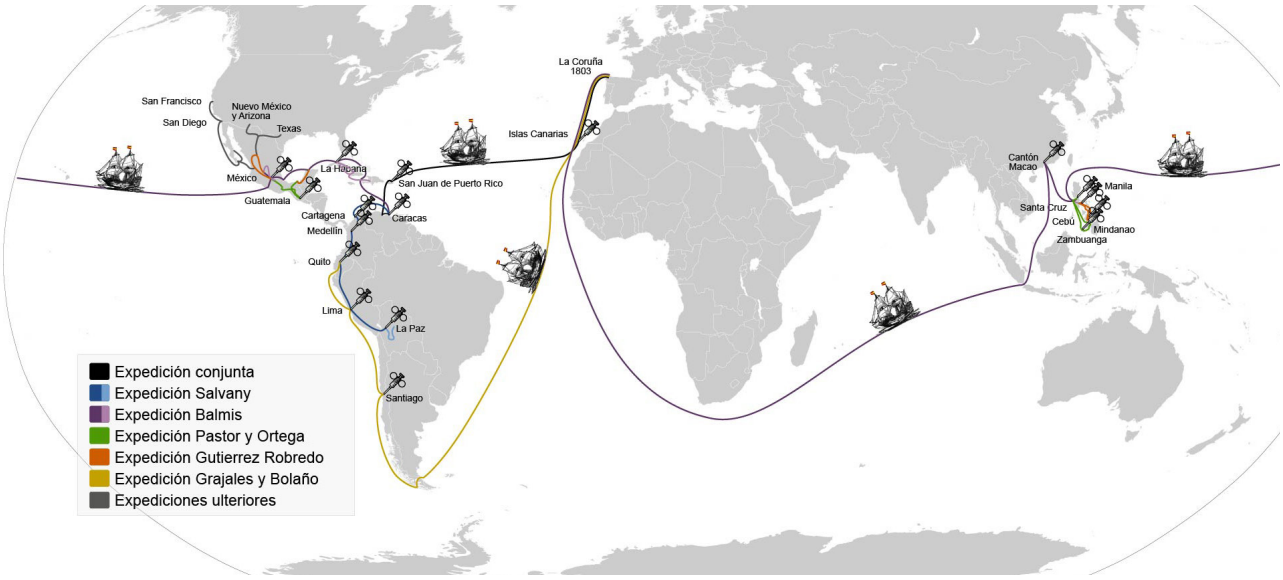
One of the Spanish groups of biotechnology companies capable of undergoing such a transformation, enabling production of sufficient initial doses and those that will be needed later, is Zendal, named after a woman linked to one of the greatest milestones in the history of vaccination worldwide.

Isabel Zendal Gómez was a key member of the Royal Philanthropic Vaccine Expedition. This expedition, which took place in the early 19th century and is considered one of the world's first international humanitarian missions, sought to expand vaccination against smallpox throughout the overseas territories under the rule of the Spanish empire at that time.

Smallpox is the only disease eradicated from the face of the earth to date, in what was the greatest success in the history of vaccines and of the WHO. But at that time, the disease caused very high mortality, especially in children. It was an epidemic that plagued the world, irrespective of social class. Perhaps this is why King Carlos IV, who had lost his daughter María Teresa to smallpox, promoted the expedition, which was financed by the Spanish Treasury.

At the end of the 18th century, the English doctor Edward Jenner observed that, among his patients, those who had been infected with cowpox were immune to human smallpox. He thus began his investigations, and inoculated individuals susceptible to smallpox with pus from patients already infected with cowpox. He found that those inoculated became immune, thereby creating the world's first vaccine. This revolutionary finding spread rapidly throughout Europe to reach Spain.

A very large smallpox outbreak in Spanish overseas territories prompted the application of Jenner's suc-



Route of the Royal Philanthropic Vaccine Expedition (Wikipedia commons, Ecelan)

cessful method to the Americas.

The person responsible for this expedition was Dr. Francisco Javier Balmis, after whom the humanitarian military operation launched in response to COVID-19 is named. Aboard the corvette María Pita, this doctor from Alicante led the expedition, which departed from La Coruña on November 30, 1803. He was accompanied by José Salvany, deputy director of the expedition, nurses, assistants, and the aforementioned Isabel Zendal, director of the La Coruña orphanage. The reason for her presence was that, since the vaccine could not be maintained at the necessary low temperatures for the duration of the voyage, the orphans themselves served as transporters of the vaccine. They acted as a human chain: each one was sequentially infected with cowpox using pus from a previously infected individual. This continued until they reached the Caribbean. The group of orphans on the María Pita consisted of 22 children who fulfilled the necessary criteria: aged 8–10 years, with no history of previous exposure to the disease. They were selected from orphanages in Madrid and La Coruña, since no families wished to send their children on the expedition. In return, the Crown promised to provide the orphans with education upon completion of the voyage, a promise that was never fulfilled. In addition to caring for the children, Isabel Zendal ended up helping with vaccinations in the New World. For her work, she was later recognized by the WHO as the first nurse to take part in an international humanitarian mission.

Despite many obstacles encountered by the expedition, the vaccine reached the Antilles, Central and South America, the Philippines, Macao, Canton, and the English island of Santa Elena. In addition, vaccination boards were created and local doctors were instructed to continue vaccinating in each territory, while the expedition continued.

This little-known but very important feat was the beginning of the history of vaccination in Spain. Moreover, it was an expression of solidarity, financed as it was by the Spanish Crown. Public health took precedence over money. In the words of Edward Jenner himself: "I don't imagine the annals of history furnish an example of philanthropy so noble, so extensive as this."

Will we be able to repeat it?

Glossary of Terms

· ACE-2: angiotensin-converting enzyme 2. This is the receptor that the SARS-CoV-2 virus uses to penetrate the cell.

· Recombinant DNA: artificial, laboratory-synthesized DNA molecule.

· Antigen: molecule of an infectious agent against which antibodies can be generated.

· Cytokines: proteins that are secreted by immune system cells and coordinate the immune response. This group of proteins includes interleukins and chemokines.

· COVID-19/SARS-CoV-2: COVID-19 is the disease (CoronaVIrus Infectious Disease-2019) caused by the virus known as SARS-CoV-2 (Severe Acute Respiratory Syndrome). The number 2 refers to the fact that this is the second coronavirus known to cause severe acute respiratory syndrome.

· S protein: also known as spike protein, is found on the outside of SARS-CoV-2 and interacts with the ACE-2 protein in human cells.

· Interleukin, interferon: different types of cytokines.

· Clinical trials: studies designed to evaluate the safety and efficacy of new treatments or vaccines in humans, after obtaining prior approval by the competent authorities.

· Chemoinformatics: discipline that focuses on the identification, development, and optimization of drugs through the use of computational techniques.

· Drug repurposing: the identification of new applications for drugs initially used to treat other diseases.

· Virtual screening: computational technique used in drug development to identify, by searching large libraries of compounds, molecules that can potentially bind to the therapeutic target of interest (proteins, enzymes).

· ARDS: acute respiratory distress syndrome.

· Cytokine storm: an altered immune response that results in excessive and uncontrolled production of cytokines, leading to an exaggerated inflammatory response that can have very serious consequences.

LINKS OF INTEREST

- **CSIC:** www.csic.es/en
- **Global Health Interdisciplinary Platform (PTI):** www.pti-saludglobal-covid19.corp.csic.es/en
- **PTI Newsletter:** www.pti-saludglobal-covid19.corp.csic.es/newsletter
- **CIB Margarita Salas:** www.cib.csic.es/
- **CIB Outreach Channel:** www.divulgacion.cib.csic.es
- **Repositorio COVID en Digital.CSIC:** www.bibliotecas.csic.es/coleccion_especial_covid19_digitalcsic
- **Spanish Health Ministry:** www.mscbs.gob.es
- **Comunidad de Madrid:** www.comunidad.madrid
- **Institute of Health Carlos III (ISCIII):** www.isciii.es
- **World Health Organization (WHO):** www.who.int
- **Solidarity Clinical Assay:** www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
- **COVID-19 Treatment and Vaccine Tracker:** www.milkeninstitute.org/covid-19-tracker
- **Asociación Española de Medicamentos y Productos Sanitarios (AEMPS):** www.aemps.gob.es/la-aemps/ultima-informacion-de-la-aemps-acerca-del-covid19
- **Sociedad Española de Virología (SEV):** www.sevirologia.es
- **Sociedad Española de Inmunología (SEI):** www.inmunologia.org

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