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Alicante-Winter Immunology Symposium in Health (A-Wish) and the Boulle-SEI awards: A collaboration between the Spanish Society for immunology, the University of Alicante and the Jean Boulle Group to honor the Balmis Expedition

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On December 16th and 17th 2021 the Spanish Society of Immunology (SEI) and the University of Alicante (UA) joined forces to organize the first Alicante-Winter Immunology Symposium in Health (A-WISH) that took place at the Auditorium of the Provincial Council of Alicante (https://a-wish.org). The main objective of this annual symposium is to promote the development and advancement of the study of immunology, infectious diseases and vaccinology, as life and health sciences, as well as to disseminate the development of novel approaches in diagnosis and therapeutics of diseases that involve the immune system. In this first edition, the international symposium aimed to address strategies for the coronavirus disease 2019 (COVID-19) response and pandemic preparedness, the development of the vaccines against the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and the immunological response to infection and COVID-19 vaccines. Researchers from both academic and pharmaceutical industry backgrounds shared their expertise and insights into the latest developments (see Figs. 1–8).

In the initial months of the pandemic, Spain was one of the countries most affected by the COVID-19. The SARS-CoV-2 had an unprecedented economic, social, health and scientific impact and represented an unparallel challenge in modern history to undertake a world-wide vaccination campaign against an emerging virus for which no previous vaccine existed. The first session of the symposium entitled "**The importance of vaccination**" focused on the history of airborne viral pandemics, the development of interdisciplinary research platforms on global health and the critical role of the regulatory agencies that approve novel vaccines. **Raul Ortiz de Lejarazu**, Emeritus Director and Scientific Advisor of the National Influenza Center, which is part of the Global Influenza Surveillance and Response System (GISRS) network of the World Health Organization (WHO) highlighted that from the 20th to the 21st century, four pandemics of different intensity and consequences have occurred, all of them caused by orthomyxovirus. The risk of zoonotic transmission and an associated new pandemic is rising substantially and health care services, drug availability, laboratory testing, research capacity and global governance have underlined significant gaps in response to COVID-19. Although the COVID-19 vaccine development has been done at unprecedented speed, Dr. Lejarazu emphasized that many challenges remain, including the large-scale production of sufficient quantity of vaccines, delivery of vaccines to all countries and ensuring vaccination of relevant age groups. This effort to vaccinate must be consistent with future pandemic, early post-pandemic and post-pandemic scenarios in which prevention measures must be accompanied by their standardization in clinical and health practice.

To address the research gaps identified during COVID-19 **Margarita del Val**, Professor at the Centro de Biología Molecular Severo Ochoa (CSIC-UAM) introduced the Global Health Research Platform of CSIC developed by the Spanish National Research Council-CSIC (https://pti-saludglobal-covid19.corp.csic.es/en/). Dr. del Val coordinates this project and highlighted that on the day the pandemic was declared by WHO, the research platform assembled an interdisciplinary network of research teams from social sciences to biomedicine, engineering and mathematics, with a clear focus on providing knowledge and practical solutions stemming from research and headed for the society. Its growth, consolidation, achievements and future goals were the subject of her

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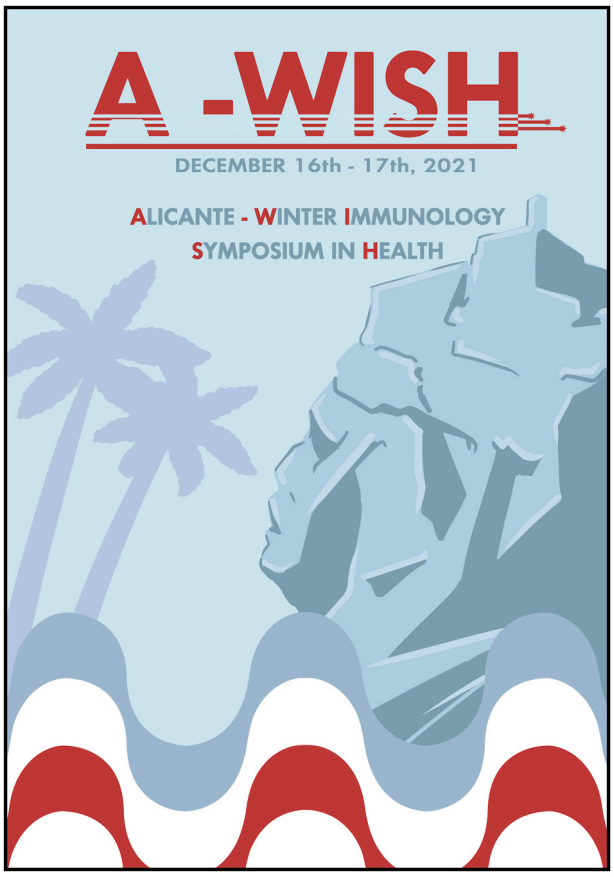

Fig. 1. A-WISH poster designed by Jordi Gonzalez.

talk. The platform mobilized and coordinated more than 300 research groups from more than 90 CSIC centers in six work packages, which seek to cover all aspects of the pandemic with an interdisciplinary approach: prevention, disease, containment and diagnosis, treatment and vaccines, social impact, and communication. The platform has coordinated 100 research projects and actions, ranging from the development of

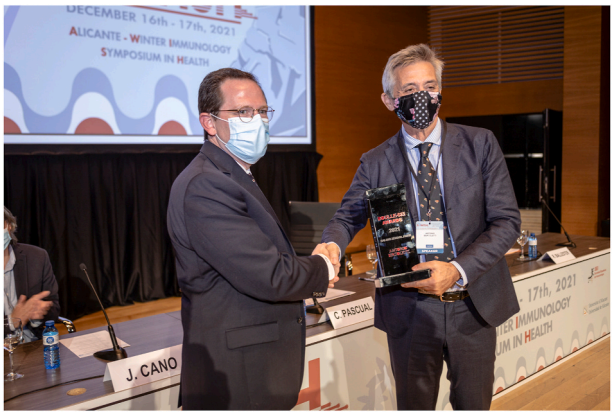

Fig. 3. Leighton Durham, representing The Boulle Group and awardee Antonio Bertoletti.

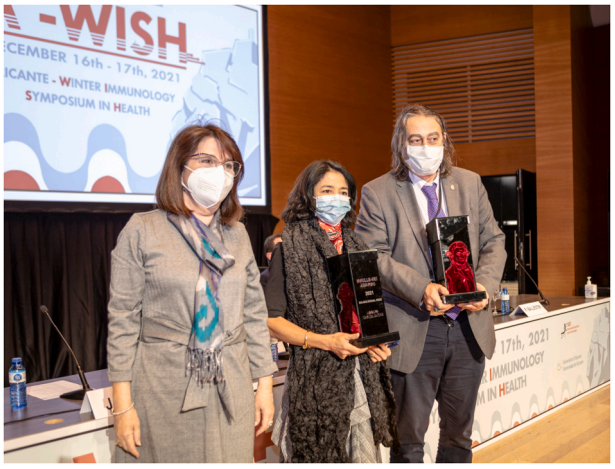

Fig. 4. Rector of the University of Alicante, Amparo Navarro with awardees Miriam Merad and Adolfo Garcia-Sastre.

Fig. 2. Awardees Sonia Zuñiga, Luis Enjuanes and Isabel Sola.

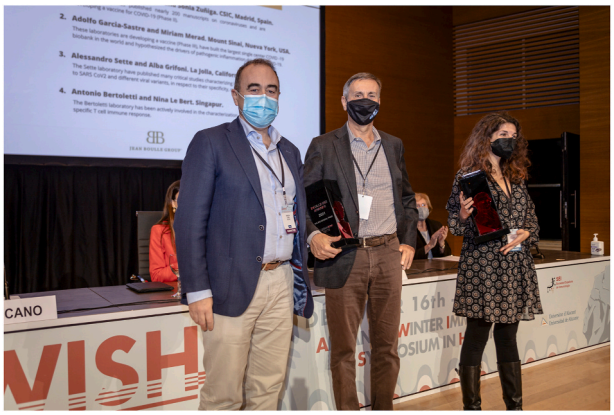

Fig. 5. SEI President, Marcos Lopez-Hoyos with awardees Alessandro Sette and Alba Grifoni.

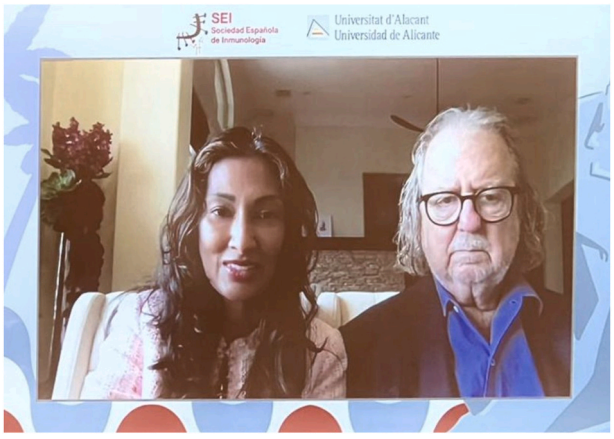

Fig. 6. Drs. Sharma and Allison announcing the names of the awardees.

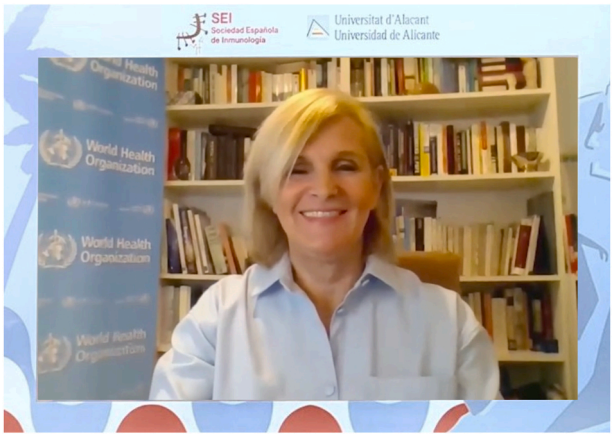

Fig. 7. Dr. Naira closed the symposium highlighting the importance of One Health.

antivirals and antiinflammatory treatments, the monitoring of transmission, the study of the virus genome and the impact of mutations, the genetics of patients, their immune response to infection and vaccination, and the marketing of systems for diagnosing and containing the virus. The platform has also included studies addressing the social perception of the measures, especially on the impact on elderly nursery homes. Therefore, the establishment of Global Health Research represent stable structures for scientific cooperation, as well as for the generation of novel technologies. Its consolidation, reinforcing its structure and coordination mechanisms, in particular the liaison with the clinical sector, prepares for new challenges and opportunities, and for the development of initiatives with companies, necessary to configure a response to this and future pandemics.

The critical role of the European Medicines Agency (EMA) in the approval vaccines against SARS-CoV-2 was discussed by **Agustin Portela,** from the Spanish Medicines and Sanitary Products Agency (AEMPS). The EMA in collaboration with other National EU Medicine Agencies aims to accelerate the development of effective measures to combat and prevent the spread of COVID-19 and have made a great achievement by authorizing, in a short period of time, four safe and efficacious COVID-19 vaccines that are controlling the SARS-CoV-2 pandemic. Therefore, the one of the main objectives of the regulatory agencies is to promote scientific excellence in the evaluation and supervision of medicinal products for the benefit of public health in the European Union, playing a central role in the fight against the COVID-19 pandemic. To achieve this goal, the EMA established dedicated working groups to address the scientific, regulatory and operational challenges created by the COVID-19 pandemic and initiated its business continuity plan. This included exploring ways to accelerate the development of COVID-19 vaccines and treatments, although the EMA's responsibility does not end with the approval of vaccines, but continues through pharmacovigilance in order to detect adverse reactions, which were not detected during the clinical trials.

1. Regional, national and European networks to monitor SARS-CoV-2 vaccination

Monitoring the immunogenicity and immunity against SARS-CoV-2 vaccination in large population-based studies requires coordination and preparedness plans comprising regional, national and European networks. **David Navarro,** Chair of the Microbiology Department at the Hospital Clinico de Valencia, discussed about the Valencian Community COVID-19 vaccine research program (ProVaVac) which main objectives are to provide scientific understanding of the effectiveness, immunity and possible adverse effects associated with COVID-19 vaccines (https://infocoronavirus.gva.es/es/provavac). To do so, the ProVaVac program established a consortium that includes representatives of hospitals, universities and research centers working under the scientific direction of David Navarro to generate knowledge, promote the coordination and integration of research projects dedicated to post-vaccination follow-up, facilitate the establishment of synergies between different entities and research groups, and offering them the data support of the Public Health System of the Valencian Community. One example of the generation of research data for public service information on the vaccination strategy was the evaluation of the immunogenicity and long-term immunity of SARS-CoV-2 mRNA vaccines among the general population and nursing home residents (Albert et al., 2022; Torres et al., 2021). The knowledge generated was then disseminated to the public and used to support health decision making and to implement strategies for high-risk patients, including administration of a third dose of Comirnaty in nursing home residents (Gimenez et al., 2022) and the overall population of the Valencian Community. The ProVaVac program is therefore a clear example of interdisciplinary public coordinated actions that generates scientific evidence to advice on the vaccination strategy, its implementation and dissemination to the public.

To discuss about national networks research networks, **Jesus Frias**, Director of the Spanish Clinical Research Network (SCReN), which is funded by the Instituto de Salud Carlos III and the European Regional Development Fund (ERDF) to support clinical investigations, highlighted the advantages of collaborative, non-profit network structures with a national scope. SCReN (https://scren.eu) is a clinical research platform made up of a set of clinical research units and their capacities to provide scientific-technical services through infrastructures and professionals belonging to different institutions nationwide. Its mission is to

guarantee the provision of transversal services to support the development of research projects included in clinical investigations and clinical trials and transfer of knowledge to the national health system. This networked structure, made up of 34 support units distributed throughout the country, has more than 100 people on staff with different profiles, which are responsible for the support of research teams in the implementation, development and monitoring more than 200 clinical research projects. One of the most recent projects is the CombiVacS study: "Immunogenicity and reactogenicity of BNT162b2 in subjects having received a first dose of ChAdOx1S: initial results of a randomised phase 2 clinical trial (CombiVacS)", a phase 2, open-label, randomised, controlled clinical trial on adults vaccinated with a single dose of ChAdOx1-S (AstraZeneca) who received a second dose of BNT162b2 (Pfizer). Results with data on 7-day reactogenicity and 14-day anti-spike IgG response, antibodies functionality and cellular immune response demonstrated safety and immunogenicity of heterologous vaccination (Borobia et al., 2021).

In addition to the Spanish approaches, the COVID-19 pandemic has highlighted the need for dynamic and strategic European preparedness plans to combat emerging epidemics and pandemics. This pandemic is only one example of the future risks we may face in the context of behavioral and climatic changes in this globalized world. During the last talk of the first session, **Dr. Jon Salmanton-García**, Postdoctoral Researcher and Project Manager at the University Hospital Cologne (Cologne, Germany) and **Dr. Zoi Dorothea**, Specialist in Pediatrics at the European University Cyprus (Nicosia, Cyprus), described the European coronavirus vaccine trial accelerator platform, also known as VACCELERATE (https://vaccelerate.eu/). Drs. Salmanton-García and Dorothea emphasized that as part of the European Union (EU) scientific community it is our responsibility to protect our future citizens by evolving and establishing coordinated scientific networks among Europe. They highlighted the urgent need to build on the European response to COVID-19 by creating, maintaining, and strengthening sustainable public health capacities for future emergency pandemic preparedness, including the vaccine development. These plans should focus on inclusiveness and access to all EU citizens, including children and other underserved minorities across Europe that has been implemented through the VACCELERATE Volunteer Registry (https://doi.org/10.1016/j.vaccine.2022.05.022). In this respect, the VACCELERATE clinical research network represents the first pan-European structure providing a single entry-point to connect all European stakeholders in COVID-19 vaccine development (pharma, academia, European Commission, European Medicines Agency [EMA], European Centre for Disease Prevention and Control [ECDC] and national health authorities) for phase clinical trials in Europe. While VACCELERATE is a European clinical research network that aims to promote the development of clinical trials to expand knowledge about vaccines against SARS-CoV-2, they are also committed to the coordinated work of the entire European scientific community to protect health in future emergencies. This network is coordinated by the University Hospital of Cologne in Germany and currently includes 29 national partners in 18 EU-member states and 5 associated countries to the EU Horizon 2020 research programme. VACCELERATE has created and launched a network of clinical trials sites throughout Europe: EUVAP (www.euvap.eu). This is a research network prepared to initiate clinical trials in any disease, age or patient groups within a relevant time frame. The aim is to provide an appropriate infrastructure capable of rapidly clinical trials by adequately evaluating the current capacity of clinical studies. As of March 2022, 474 sites are part of this initiative, active in 41 countries. Under the VACCELERATE umbrella there are currently 3 clinical trials to: 1) evaluate immunogenicity and reactogenicity of different COVID-19 vaccines administration in older adults (≥75) already vaccinated against SARS-CoV-2 (EU-COVAT-1 AGED), 2) to determine the timing of and immunogenicity of administering a 3rd homologous mRNA vaccination dose against SARS-CoV-2 in the general population (BOOSTAVAC), and 3) to evaluate the immunogenicity and reactogenicity of reduced COVID-19 mRNA vaccination regimens in children after 1st normal dose or SARS-COV-2 infection (EU-COVPT-1 COVACC). An additional effort of the VACCERATE network is the implementation of a harmonized and sustainable Volunteer Registry in the European Region permitting a prompt identification of eligible participants for clinical trials, with a preliminary focus on COVID-19 vaccine trials. Currently, more than 12 countries have joined this effort and the registry already includes more than 36,000 volunteers. For the long-term sustainability of the VACCELERATE Volunteer registry, synergies with existing European infrastructures are currently explored. The registry may also service any future European epidemic/pandemic and health crisis, under the mandate of the EU Health Emergency Preparedness and Response Authority (HERA) Incubator initiative. The VACCELERATE Registry aims to provide a central volunteer trial platform serving as a single entry-point for stakeholders in the European region. A strategic plan of VACCELERATE focuses on inclusiveness and capacity building,

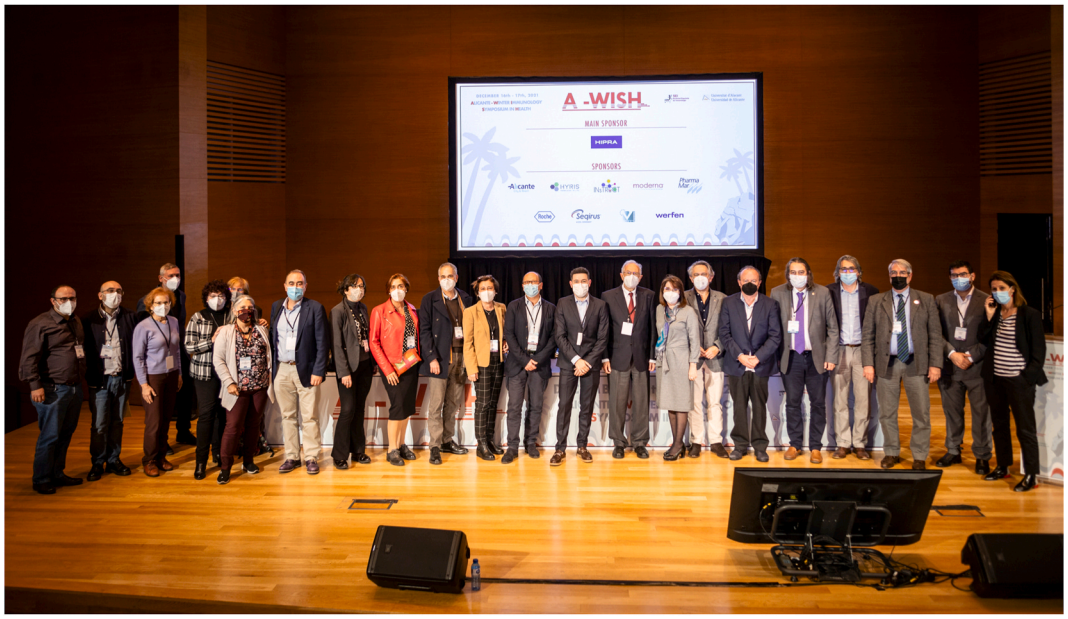

Fig. 8. Executive, Organizing, and Scientific Committees with speakers ad awardees.

expanding the registry to reach healthy individuals (adults and pediatrics), patients and underserved populations. Thus, the added values of the VACCELERATE registry lie in the specific expertise needed for clinical trials, combined with access to volunteers with or without comorbidities, and the capacity to enroll a high number of participants at a local (national) and Pan-European level within a short period of time.

Moderated by Africa Gonzalez, Raúl Ortiz de Lejarazu, Margarita del Val, Agustín Portela, David Navarro, Jesús Frías, Zoi Dorothea and Jon Salmanton-García, addressed the major challenges that they faced during the COVID-19 pandemic during **Round Table 1**. In general, major challenges included the difficulty of placing science in the center of public health decisions rather than financial cost-benefit parameters. In addition, the reasons behind vaccination hesitancy were also discussed along with proposals to improve vaccination rates that mainly focused on developing clear and honest communication channels with the general population. One of the controversial questions was vaccination in children, which requires parental approval. Zoi Dorothea highlighted the benefits of SARS-CoV-2 vaccination in pediatric individuals for their own benefits and questioned the argument supporting vaccination of children to protect adults and the general population: "it would be the first time in history that we vaccinate part of the population to protect others".

2. COVID-19 vaccines (1)

Vaccine development represents a critical component for controlling the ongoing SARSCoV-2 pandemic and three of the main Spanish virologists presented their vaccine models on the second day of the symposium. Luis Enjuanes, leader of the replication, virus-host interactions, and protection in coronavirus laboratory at the Centro Nacional de Biotecnología (CNB–CSIC) summarized the main characteristics of the seven virus of the Coronaviridae family that cause zoonoses (human infections of animal origin); four already attenuated (HCoV-OC43, HCoV-229E, HCoV-NL-63, HCoV-HKU1) and three deadly for humans (SARS-CoV, MERS-CoV and SARS-CoV-2). These viruses have the ability to cross the species barrier from wild bats to humans, through an intermediate host that has not yet been described for SARS-CoV-2. Dr. Enjuanes went on to describe that Coronaviruses use conserved mammalian cell machinery for entry and have a unique capacity for adaptation to novel host environments. Consequently, human coronaviruses are the cause of up 15% of all respiratory infections. One important aspect that was covered in this talk was the origin of the SARS-CoV-2 as a mean to prevent potential transmission in the future. Dr. Enjuanes argued against the COVID-19 lab leak theory, which proposes that SARS-CoV-2 originated from the Wuhan Institute of Virology (WIV) in China. The Wuhan Wildlife Market, where the pandemic originated, is located north of the Yangtze River, while the WIV is located south of the river, so the hypothesis that this virus could be part of scientific experiments conducted at WIV is unlikely. More science is needed to determine how SARS-CoV-2 reached humans (Calisher et al., 2021). In the second part of his talk, Dr Enjuanes mentioned that his group, which includes Isabel Sola and Sonia Zuñiga, has been studying the molecular basis of coronavirus replication and virulence for more than twenty years to identify signaling pathways that can be used as potential targets. This knowledge has allowed them to delete the envelope (E) and non-specific protein 1 (nsp1) genes from the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV producing a replication-competent propagation-defective RNA replicon (Gutierrez-Alvarez et al., 2021; Jimenez-Guardeno et al., 2015). Self-amplifying RNA replicons are promising platforms for vaccine development as they are essential for viral replication, particle assembly, or dissemination. Luis Enjuanes and his team are currently working with SARS-CoV-2 replicons coated with nanoparticles that induce sterilizing immunity and significant levels of neutralizing antibodies in mice. Development of SARS-CoV-2 vaccines with the capacity to induce sterilizing immunity is crucial to change the course of the COVID-19 pandemic.

One critical obstacle to deliver and distribute vaccines against COVID-19 in low-income countries is the requirement for transportation and storage under low temperatures. This represents a major challenge for Adolfo García-Sastre, Professor at the Department of Microbiology and Director of the Global Health and Emerging Pathogens Institute at Mount Sinai School of Medicine in New York. Dr. Garcia-Sastre, together with Drs. Peter Palese and Florian Krammer propose to develop a vaccine based on Newcastle disease virus (NDV). NDV-based vaccines for COVID-19 have several advantages as a) there is no pre-existing immunity in humans; b) it would be generated from an existing technology used to generate influenza vaccines; and c) there are clinical studies that demonstrate a good safety profile (Sun et al., 2020a, 2020b). In pre-clinical studies using animal models, the NDV-based vaccine results in abortive infection and reduced viral replication in lung and nasal mucosa due to the induction of a robust local innate immune response while generating high levels of antibodies against SARS-CoV-2 (Tcheou et al., 2021). In contrast to adenovirus vector vaccines, NDV-based vaccines not only express the vaccine antigen in infected cells, but also incorporate the antigen into the virion, making it possible the use of either live or inactivated versions of the vaccine. These results supported phase I/II clinical trials initiated in Vietnam, Thailand, Mexico and Brazil, where it demonstrates good safety and immunogenicity profiles. Preliminary results demonstrate lack of severe adverse events and poor reactogenicity, as well as induction of a robust T cell and neutralizing antibody responses against SARS-CoV-2 (Pitisuttithum et al., 2021). Additional clinical trials have been initiated using both intramuscular and intranasal live administration, which has the potential to generate potent mucosal immunity for prevention of asymptomatic infection and transmission. Importantly, the NDV-based vaccines can be manufactured locally in developing countries and be transported and distributed refrigerated at 4 °C to reach vaccination pods.

Although the concept of using mRNAs as vaccines was introduced over 30 years ago, it did not revealed a real potential until the emergence of SARS-CoV-2 pandemic in December 2019. Both SARS-CoV-2 mRNA-based vaccines (BNT162b1 from Pfizer-BioNTech and mRNA-1273 from Moderna) demonstrated ~95% efficacy in preventing COVID-19. In Spain, the group of Felipe García at the IDIBAPS/Hospital Clinic de Barcelona of has previous experience on this technology, as they have ongoing phase I/II clinical trials with a mRNA-based vaccine against HIV (de Jong et al., 2019; Leal et al., 2018) and lead the COVARNA consortium an the preclinical development of innovative mRNA/MVA vaccines against SARS-CoV2, with the participation of the partners Universidad Barcelona, Universidad Pompeu Fabra, Centro Nacional Biología-Centro Superior de Investigaciones Científicas, Universidad Santiago de Compostela and Université Libre de Bruxelles (https://ods.cat/en/preclinical-development-of-innovative-mrna-mva-vaccines-against-sars-cov2/). Montserrat Plana Prades, accredited researcher at IDIBAPS, summarized the objectives of COVARNA consortium to develop a vaccine against SARS-CoV2 based on mRNA through an innovative strategy. Using computational biological methods, they designed and produced S protein sequences that induce B cell and T cell responses to HLA-I and HLA-II epitopes. Moreover, they produced nanocarriers capable of improving the stability and transport of mRNA into the target cells. Preliminary data demonstrated RBD expression in monocyte-derived dendritic cells associated to high levels of neutralizing antibodies achieving long-term immunity against SARS-CoV-2 in mice. Once the development of a vaccine capable of generating a potent humoral and cellular response was demonstrated their proposed roadmap includes evaluation of the safety and efficacy of the vaccine in humans and the design of new mRNA sequences against potential Variants of Concern (VoC).

Respiratory failure due to SARS-CoV-2 has caused widespread mortality, creating an urgent need for effective antivirals treatments, such as remdesivir and molnupiravir. José María Fernández Sousa-Faro,

president of PharmaMar, introduced the use of Plitidepsin to treat SARS-CoV-2 infections. PharmaMar is a pioneer company that focuses on marine-based cancer medicines for over thirty years. Plitidepsin is extracted from the ascidian *Aplidium albicans*, which is exclusively found in the waters of Es Vedrà, an uninhabited island of the southwest coast of Ibiza in the Mediterranean Sea. Mechanistically, plitidepsin is an inhibitor of the Eukaryotic Translation Elongation Factor 1A (eEF1A), which delivers aminoacyl-tRNAs to the ribosomal A-site during protein synthesis. In cancer cells plitidepsin leads to cell-cycle arrest and induction of apoptosis via multiple pathways. The eEF1A protein is crucial for the formation of double-membrane vesicles that are needed for the propagation of the SARS-CoV-2. This functional activity against SARS-CoV-2 has been demonstrated in mouse models with a potent antiviral activity with limited toxicity (90% inhibitory concentration = 0.88 nM) (White et al., 2021). Given the promising results obtained at the preclinical level, Dr. Fernandez Sousa-Faro and his team at Pharma Mar started a phase I/II dose-escalating clinical trial, which proved the efficiency of the treatment, especially in patients with moderate infection (Varona et al., 2021, 2022). Given these results, PharmaMar recently obtained authorization to start a phase III clinical trial (NEPTUNO) to determine the efficacy of plitidepsin for the treatment of hospitalized patients with moderate COVID-19 infection.

In Round Table 2, Maria Montoya, Luis Enjuanes, Isabel Sola, Sonia Zuñiga, Adolfo García-Sastre, Montserrat Plana and José María Fernández Sousa-Faro discussed multiple points under the moderation of Ana Fernandez-Sesma. First, Dr. Montoya explained the work from Vicente Larraga at the Margarita Salas Biological Research Center (CIB–CSIC). The Molecular Parasitology Group led by Dr. Larraga has developed a recombinant DNA-based vaccine against canine Leishmaniasis that is currently in Phase IV, and they have used this platform to design a synthetic DNA plasmid (pPAL) that allows the integration of SARS-CoV-2 antigens into human cells (Alcolea et al., 2019). This vaccine has the advantages that it is not selected with antibiotics, can be stored at room temperature and can be adapted as new variants emerge. On the other hand, Dr. JM Fernández provided further explanation on the mechanisms of action of plitidepsin and described that adverse effects are mainly nausea and vomiting, but patients respond well to antiemetic medication. Dr. Garcia-Sastre had the opportunity to discuss the kinetics of the replication capacity of the Omicron variant versus the response of immunized individuals. The challenge of mucosal immunity against SARS-CoV-2 was addressed by Dr. Enjuanes along with Drs. Sola and Zuñiga, who explained the advantages of their vaccine in generating immunity against multiple SARS-CoV-2 proteins and how that could be beneficial even in people already immunized with other vaccines. In addition, multiple panelists discussed the value of generating vaccines against more conserved antigens. Finally, Dr. Garcia-Sastre made an important reflection: the COVID-19 pandemic is generating a multitude of data on respiratory infections, primary infections and reinfections. By working in a coordinated manner, we could better understand multiple immunological mechanisms such as T cell memory, B cell memory diversification, repertoire generation, affinity maturation and other immunologically relevant issues. As immunologists, we must seize this unique opportunity.

3. COVID-19 vaccines (2)

The third session of the symposium continued on COVID-19 vaccines, highlighting the critical contribution of pharmaceutical companies. Antoni Prenafeta, Senior Manager for the development of new vaccines in the R&D Department of HIPRA (Spain), elaborated on the crucial role of vaccines in the decline of new infection rates, prevention of severe disease and more importantly, the outstanding decrease in mortality rates. In parallel Dr. Prenafeta indicated that new VoC are continuously evolving, arguing in favor to the development of accessible second-generation COVID-19 vaccines against known and future VoC to mitigate the current pandemic. Dr. Prenafeta provided preclinical and clinical data showing the immunogenicity, efficacy, and safety results of a receptor-binding domain (RBD)-based recombinant protein vaccine candidate (PHH–1V) which consists of a novel RBD fusion heterodimer containing the B.1.1.7 (alpha) and B.1.351 (beta) variants of SARS-CoV-2, formulated with an oil-based adjuvant equivalent to MF59C.1. In preclinical studies, PHH-1V immunization of BALB/c mice induced RBD-binding antibodies with neutralizing activity against the alpha, beta, gamma, and delta variants. Furthermore, vaccination of mice elicited robust activation of $CD4^+$ and $CD8^+$ T cells with early expression of Th1 cytokines upon *in vitro* restimulation, along with a 100% efficacy with either 10 mg and 20 mg in k18-hACE2 mice exposed to SARS-CoV-2 associated with a good tolerability profile (Barreiro et al., 2011). In phase I/IIa clinical studies, the PHH-1V has demonstrated a very good safety profile with induction of binding and neutralizing antibodies against all VoC and IFN-γ specific cellular immune response. Results presented at this session showed the viability of this new approach of recombinant vaccine that includes two different RBD in the same vaccine. More importantly, this platform is easy to adapt to new VoC with a good stability that guarantees global distribution and access world-wide.

BNT162b2 (Pfizer–BioNTech) is a COVID-19 vaccine containing nucleoside-modified mRNA encoding the SARS-CoV-2 spike glycoprotein, which represents the most extensively administered vaccine in Spain. Cristina Méndez Díaz, Senior Medical Director Southern Europe (Pfizer Vaccines MDSCA, IDM), reviewed the most relevant aspects of the BNT162b2 vaccine, including the two-dose randomized controlled trial (RCT) showing 95% or greater efficacy against symptomatic and severe COVID-19 disease in individuals from 16 years old and older (Polack et al., 2020). In addition, Dr. Méndez presented data about the effectiveness of BNT162b2 in the real-world setting and the large public health effect on reducing infections, hospital admissions, and deaths at a time when the alpha (B.1.1.7) variant was the predominant strain (Petter et al., 2008). Dr. Méndez went on to discuss the concern raised by the continuous emergence of VoC on the vaccine efficacy, but provided evidence of significant amounts of neutralizing antibodies against all variants evaluated before Omicron. Waning effectiveness demonstrated by lower neutralizing antibody titers and an increased number of infections 6–12 months after the second dose was a strong argument for potential booster doses in adults with high-risk conditions (i.e. elderly or immunodeficient). Dr. Méndez showed evidence from Israel for the protection from breakthroughs after a third booster dose (Bar-On et al., 2021; Barda et al., 2021). Finally, evaluation of BNT162b2 in other age groups such as younger adolescents was discussed. The incidence of COVID-19 is reported to be higher among 12-to-17-year-old adolescents than among younger children. In addition, children, especially from low-income families, have been negatively affected by the lack of in-person learning during the pandemic. Therefore, a demonstration of efficacy and safety in 12-to-17-year-old adolescents was important to expand the conditional market authorization and include children 12 years of age or older, which represents a critical step toward achieving herd immunity.

Next presentations were about measuring cellular immunity to SARS-CoV2 as a new challenge for all actors involved in the current pandemic phase. From vaccine manufacturers to public health institutions, the most common tool available to measure the immune response is antibody testing. However, evidence demonstrates that antibody testing provides only a partial view of the immunity against COVID-19, since individuals with potential exposure to SARS-CoV-2 or vaccinated do not necessarily develop or maintain antibody positivity. Cellular immunity is a critical component to prevent pathogen spread as an additional defense for the immune system and testing T cell immunity represents an important element to consider to better manage and monitor the COVID-19 pandemic. However, the complexity and lack of scalability of traditional methods to measure the cellular immune response have prevented the establishment of T cell immunity diagnostic tests into the routine clinical practice. Stefano Lo Priore, founder and CEO of Hyris, explained an innovative technology to evaluate T cell

immunity in COVID-19 recovered and vaccinated individuals using a quantitative PCR method to detect cytokines after whole-blood SARS-CoV-2 specific stimulation. This novel approach can be customized to measure the cellular response against any virus variant when using different peptide pools from VoC, which is particularly important in high-risk populations such as immunocompromised patients or those with other pathologies such as cancer. Examples of studies carried out by this technology include the evaluation of the cellular immunity in response to booster vaccines in older adults (>65 years) by the Instituto de Salud Carlos III, as well as clinical trials of the VACCELERATE consortium mentioned above. Ernesto Guccione, Professor of Oncological Sciences at the Icahn School of Medicine at Mount Sinai in New York, described in detail the technique. The direct qPCR-based rapid T cell activation (dqTAC*T*) assay is based on *ex vivo* stimulation of whole blood samples with a pool of viral peptides, followed by direct amplification of *IFNG* or *IL2*, which are produced by SARS-CoV-2 antigen-specific T cells, and *CXCL10,* which is produced by monocytes and neutrophils in response to T cell activation. Dr. Guccione confirmed significant correlation between dqTACT and other traditional methods such as ELISA and ELISpot when measuring cytokine levels. Importantly, dqTACT does not need erythrocytes lysis or RNA purification, which minimizes time and handling errors, favoring its translation into the clinic.

Round Table 3 was moderated by Estanislao Nistal. Antoni Prenafeta, Cristina Méndez, Ernesto Guccione, Stefano Lo Priore and Toni Lloret started discussing about the difficulty to differentiate between $CD4^+$ and $CD8^+$ T cell responses with the dqPCR technique and the use of 15-mers peptides. Dr. Lloret briefly commented on the possibility of developing mRNA-based influenza vaccines. However, the central topic of discussion was the third dose of the COVID-19 vaccine.

Although studies were cited showing that booster doses increase the number of neutralizing antibodies, additional studies assessing the cellular response to SARS-CoV-2 vaccination are yet to be performed for a complete evaluation of the immune response. Thereafter, an intense debate came from the audience on topics such as durability, boosters (dose, number, periodicity), personalized or mass vaccination, inclusion of VoC in multivalent vaccines, or the need of sterilizing vaccines. The experts agreed that the 3rd dose should be recommended based on.

Risk-benefit analysis of COVID-19 vaccines, but that future immunological studies are necessary for additional boosters. Importantly, although the final decision rests within health authorities, immunologists should lay the foundations of knowledge and provide advice to public regulatory agencies. Finally, it was also debated whether it would be more effective in controlling the pandemic to focus on vaccinating developing countries. In this respect, Dr. Cristina Méndez stated that governments and companies, including Pfizer, are collaborating in the COVID-19 Vaccines Global Access, (COVAX) alliance to provide vaccines in low-income countries. Unfortunately, the limited logistical capacity of these countries remains a hurdle to deliver millions of vaccine doses in remote areas.

4. COVID-19 and the immune response

Alessandro Sette, Head of the La Jolla Institute for Immunology (LJI) Division of Vaccine Discovery and Chair of the Institute Center for Infectious Diseases, began his presentation on the adaptive immune responses to SARS-CoV-2 acknowledging the critical work of Alba Grifoni, Shane Crotty and Daniela Weiskopf that contributed to the rapid generation of knowledge demonstrating that the immune response generated against SARS-CoV-2 involves both the humoral and cellular immune response (Grifoni et al., 2020a, 2020b). The Sette laboratory developed specific SARS-CoV-2 peptides and demonstrated that in early stages of infection patients with less severe disease first exhibit a $CD4^+$ T response, followed by $CD8^+$ T cells and finally antibodies, confirming that cell surface SARS-CoV-2 antigens trigger potent immune responses (Rydyznski Moderbacher et al., 2020). However, other antigens in addition to spike were also identified to promote strong immune responses, indicating that a broad spectrum of T cells develop in response to natural SARS-CoV-2 infection. The duration of this natural immunity has been described to be 6–8 months and is similar to that generated with vaccines with no major differences between older and younger individuals (Dan et al., 2021). Dr. Sette also discussed about the "immune history" of subjects that they include in their studies and noted pre-existing immunity in unexposed individuals, due to the homology of SARS-CoV-2 with other coronaviruses, such as the common cold (Mateus et al., 2020), which is associated with an earlier immune response that helps to combat the infection generated by this new coronavirus (Sette and Crotty, 2020). In addition, Dr. Sette argued in favor of the "hybrid immunity" as more potent than either vaccination or infection alone and its relevance in breakthrough infections. Another fundamental issue addressed by Dr. Sette was the next pandemic and the potential development of "pan-corona" or "pan-sarveco" vaccines using conserved cross-reactive T cells that may be used as vaccines to prevent severe disease or death. Finally, Dr. Sette addressed the critical question of VoC and their escape from the immune response in vaccinated individuals indicating that bioinformatic studies show that the different SARS-CoV-2 variants do not escape the cellular immune response, due to the great variety of recognized epitopes in each individual (93% and 97% of CD4 CD8 epitopes are 100% conserved across variants). With regards to Omicron with more mutations, the data suggests that conservation of T cell epitopes for SARS-CoV-2 spike are 72% for CD4 and 86% for CD8 (Tarke et al., 2022), arguing in favor that the vast majority of epitopes are still conserved. Importantly, the majority of mutated $CD8^+$ T cell epitopes in Omicron are still able to bind HLA class I molecules. Therefore, it is very difficult for the coronavirus to mutate sufficiently to escape the CD4 and CD8 T cell responses. In conclusion, Dr. Sette suggested that understanding antibodies, together with memory CD4 and CD8 T cells, are critical for controlling SARS-CoV-2 infection.

Antonio Bertoletti, Professor at the Emerging Viral Disease Program at Duke-NUS Medical School, began his presentation on the protective role of SARS-CoV-2 T cells by reminding us that SARS-CoV-2 is a virus belonging to the Coronaviridae family, genus Betacoronavirus, subgenus Sarbecovirus, species SARS virus and is the etiologic agent of COVID-19. Dr. Bertoletti acknowledged that infection with SARS-CoV-2 triggers an adaptive immunity in the host resulting in the production of virus-specific antibodies and T-lymphocytes. For most of the course of the pandemic, a leading role has been attributed to antibody-producing cells, where the kinetic and quantitative aspects of antibodies have been analyzed in large cohorts of patients, while information on SARS-CoV-2 specific T cells is still scarce. Dr. Bertoletti presented early data which indicated that SARS-CoV-2 specific T cells are present in uninfected individuals since infection with betacoronaviruses induces multi-specific and long-lasting T cell immunity against the structural N protein shared by coronaviruses (Le Bert et al., 2020). However, he emphasized that early onset, multiple specificity and functionality of SARS-CoV-2 specific T cells are associated with accelerated viral clearance and protection against severe COVID-19 (Tan et al., 2021). Although further studies are needed, the study suggested that early appearance of virus-specific T cells plays a key role in controlling the SARS-CoV-2 infection and correlates with early clearance of the disease. Finally, Dr. Bertoletti presented their collaborative work where they demonstrated that T cells can contribute to the rapid elimination of SARS-CoV-2 in the absence of humoral response. Specifically, the study demonstrated presence of pre-existing memory T cells that mediate cross-protection against SARS-CoV-2, which control viral replication and contribute to abort infection. Investigating early replication-transcription complexes (RTCs) Bertoletti and colleagues identified an increase in the interferon alpha-inducible protein 27 (IFI27) associated with a region of high sequence conservation of the NSP-12 among human seasonal coronaviruses (Swadling et al., 2022). These data demonstrate that expansion of polymerase (NSP-12) specific T cells may be used as cell therapy against coronaviruses arguing for their inclusion and assessment in next-generation vaccines.

Miriam Merad, Director of the Precision Immunology Institute at Mount Sinai School of Medicine in New York and the Director of the Mount Sinai Human Immune Monitoring Center (HIMC), was the last speaker of the symposium and started her presentation by highlighting the importance of designing sample-collection protocols that serve as the backbone for COVID-19 research (Charney et al., 2020). Dr. Merad discussed about the factors related to the severity of COVID-19 disease, highlighting that the course of the disease is very heterogeneous. Most people manifest moderate or asymptomatic disease, while only 20% of adults have severe disease that can lead to death. The main factor associated with more severe disease is age, although obesity, diabetes or previous organ transplantation are factors to be considered. Dr. Merad also mentioned that correlations between viral loads and patient outcomes have been evaluated in few autopsy-based studies describing small amounts of virus in different tissues, suggesting that organ failure does not appear to be related to virus-induced damage (Bryce et al., 2021). Although low titers of antibodies to SARS-CoV-2 on the day of hospitalization have been reported to be associated with a worse prognosis, lack of antibody response does not appear to be the main cause of mortality. Analyzing inflammation-related cytokines, it has been observed that high levels of TNF and IL-6 at the onset of hospitalization are good predictors of COVID-19 severity (Carbonell et al., 2021; Merad et al., 2021). This prompted the use of anti-inflammatory and immune-modulating agents as therapy, showing benefit in some patients (Del Valle et al., 2020; Merad and Martin, 2020). Dr. Merad discussed in more detail the analysis of COVID-19 patients at the time of admission and described three groups of patients with different patterns of inflammation that are associated with disease severity and worse clinical prognosis. Group 3, with greater severity, showed significantly lower levels of antigen-presenting cells and $CD8^+$ T lymphocytes and higher levels of neutrophils and monocytes (Beckmann et al., 2021). In fact, this group 3 was characterized by a unique myeloid profile characterized by the accumulation of immature monocytes with low HLA-DR and high S100A12 expression in the blood and lung tissue of patients. This induces an alteration of the resident macrophage compartment of the lung in most of the severe patients (Chen et al., 2022). Taken together, all data suggest that factors such as age, obesity or diabetes together with a delayed antiviral response, excessive myelopoiesis and vascular damage promote an immune imbalance characterized by excessive release of pro-inflammatory cytokines and hyper-inflammation that becomes pathogenic and participates in the most severe forms of the disease. This session was moderated by Dr. Florent Ginhoux, but due to time constraints the round table had to be cancelled.

5. The BOULLE-SEI awards: honoring the Balmis Expedition

The foundation of our health care systems has undergone an enormous challenge in recent months due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused the coronavirus disease (COVID-19). The health and social impact of these public health problems should lead us to recognize of the importance of research, diagnosis and prevention of infectious diseases through vaccination.

The greatest Spanish contribution to humanity in healthcare was promoted by the military and surgeon from Alicante (Spain) Francisco Balmis, who led the Royal Philanthropic Vaccine Expedition in response to a large outbreak of smallpox in the Spanish colonies. This milestone marked the first worldwide intercontinental vaccination campaign. It is calculated that the vaccination of the Canary Islands, Cuba, Puerto Rico, Venezuela, Colombia, Ecuador, Peru, New Spain (Mexico, Central America and the southwest of the current United States), Chile, Argentina, the Philippines, China, South Africa and Guinea against smallpox that saved thousands of human lives during an expedition that took place 145 years before the creation of the World Health Organization (Franco-Paredes et al., 2005; Mark and Rigau-Perez, 2009).

Edward Jenner wrote about the expedition, “I cannot imagine that in the annals of history a nobler and wider example of philanthropy than this is provided”. Alexander von Humboldt wrote in 1825: " This trip will remain the most memorable in the annals of history and the name of José Balmis must be written in the sciences with silver letters”.

In the context of the A-WISH symposium, we believed that it is essential to give social recognition to the work of research, diagnosis and vaccination against infectious diseases through the creation of the Boulle-SEI Awards, which recognizes international research teams who have contributed with their work to the treatment and prevention of vaccine-eligible diseases. The Awards are intended to recognize research exercised by the team behind the work, rather than the individual. In addition, Francisco Balmis could not have completed his expedition without Isabel Zendal and therefore, the selection of the candidate teams took into account the gender perspective, highlighting the importance of women leadership in teamwork.

The Boulle-SEI Awards have been founded by the Jean Boulle Group and The Spanish Society of Immunology (SEI) because of their shared vision to acknowledge and support the life changing work of today’s health care and life sciences community. The Jean Boulle Group’s interests span a wide range of areas, but it is principally active in natural resources, medical technology, therapeutics, and philanthropy and funded the Boulle-SEI Awards with $100.000.

The jury of the awards are international scientist of accredited prestige appointed by the SEI and includes: Sir Marc Feldmann, Professor at the University of Oxford; Maria Neira: Director of Department of Environment, Climate Change and Health at the World Health Organization (WHO); Gabriel Nunez, Endowed Professor of Pathology at the University of Michigan; Laurance Zitvogel, Group Leader of Tumour immunology and immunotherapy of cancer at Institut Gustave Roussy; Jose Villadangos, Professor in the Department of Microbiology and Immunology at the University of Melbourne; Jacques Banchereau, Professor and Director of Immunological Sciences at The Jackson Laboratory for Genomic Medicine; Kathryn Wood, Professor of Immunology in the Nuffield Department of Surgical Sciences at the University of Oxford; Alain Fischer, Director of the Pediatric Immunology Unit at Hôpital Necker-Enfants malades, Padmanee Sharma, Professor of Genitourinary Medical Oncology and Immunology at University of Texas MD Anderson Cancer Center; and James Allison, Professor and Chair of the Department of Immunology at the University of Texas MD Anderson Cancer Center.

The jury considered that international collaborative research working synergistically in different aspects of SARS-CoV-2, such as understating the mechanisms of coronavirus disease, development of vaccines and the characterization of the innate, humoral and cellular immune response, are critical to design public health programs aimed at preventing the spread of SARS-CoV-2 and end the COVID-19 pandemic. The same way that the Balmis Expedition extended smallpox virus vaccination from Spain to America and Asia, the jury decided to recognize teams in Spain, America and Asia. Announced by Drs. Sharma and Allison, the 2021 winners were selected from a global community of research scientists including Luis Enjuanes, Isabel Sola, and Sonia Zuñiga (Madrid, Spain) for their contribution to the understanding of the molecular basis of coronavirus pathogenicity; Miriam Merad and Adolfo Garcia-Sastre (NYC, USA) for identifying the drivers of disease severity and the molecular nature of pathogenic inflammation and the development of a “local” SARS-CoV-2 vaccine; Alba Grifoni and Alessandro Sette (La Jolla, USA) for characterizing the immune response in both natural infection and vaccination; and Antonio Bertoletti and Nina Le Bert (Singapore) for the developed of an innovative diagnostic test to assess the cellular response to SARS-CoV-2 infection in whole blood, which is has been used to uncover critical aspects of SARS-CoV-2-specific T-cell immune responses. At the end of the ceremony, Dr. Neira addressed the awardees and participants of the symposium to highlight the importance of coordinated, collaborative and multidisciplinary research approaches to address health risks that originate at the animal-human-ecosystems interface.

In conclusion, this first A-WISH symposium addressed strategies for COVID-19 pandemic preparedness, the development of SARS-CoV-2 vaccines the immunological response to infection and vaccination. In this Symposium, we also acknowledged the work on research, diagnosis and vaccination against infectious diseases through the creation of the Boulle-SEI Awards for internationally recognized scientific teams that have contributed to the treatment of vaccine-preventable diseases.

On behalf of the Executive, Organizing, and Scientific Committees we would like to announce the second edition of the A-WISH will be a joint international event with the "New Frontiers in Innate Immune Memory' symposium held annually in Nijmegen, which will take place in Alicante on December 14–16th 2022 (https://a-wish.org). Co-organized by Drs. Mihai Netea (Radboud University Medical Center, The Netherlands) and Paloma Riquelme (University Medical Center Regensburg, Germany), this joint international symposium will focus on Innate Immunity: Metabolism, Epigenetics and Memory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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