The SIICA SCHOOL of IMMUNOLOGY 2020

Viral immunology & Vaccinology

#SoI2.0 in live streaming

TASK ASSIGNMENT COLLECTION

We will all remember this atypical version of the SIICA School of Immunology, not so much because it was organized as an online event on a platform unknown to most of us, but because of the particular context in which it took place. All of a sudden our days made of experiments, meetings, deadlines, and much more were upset by a virus that we all would like to get rid of as soon as possible.

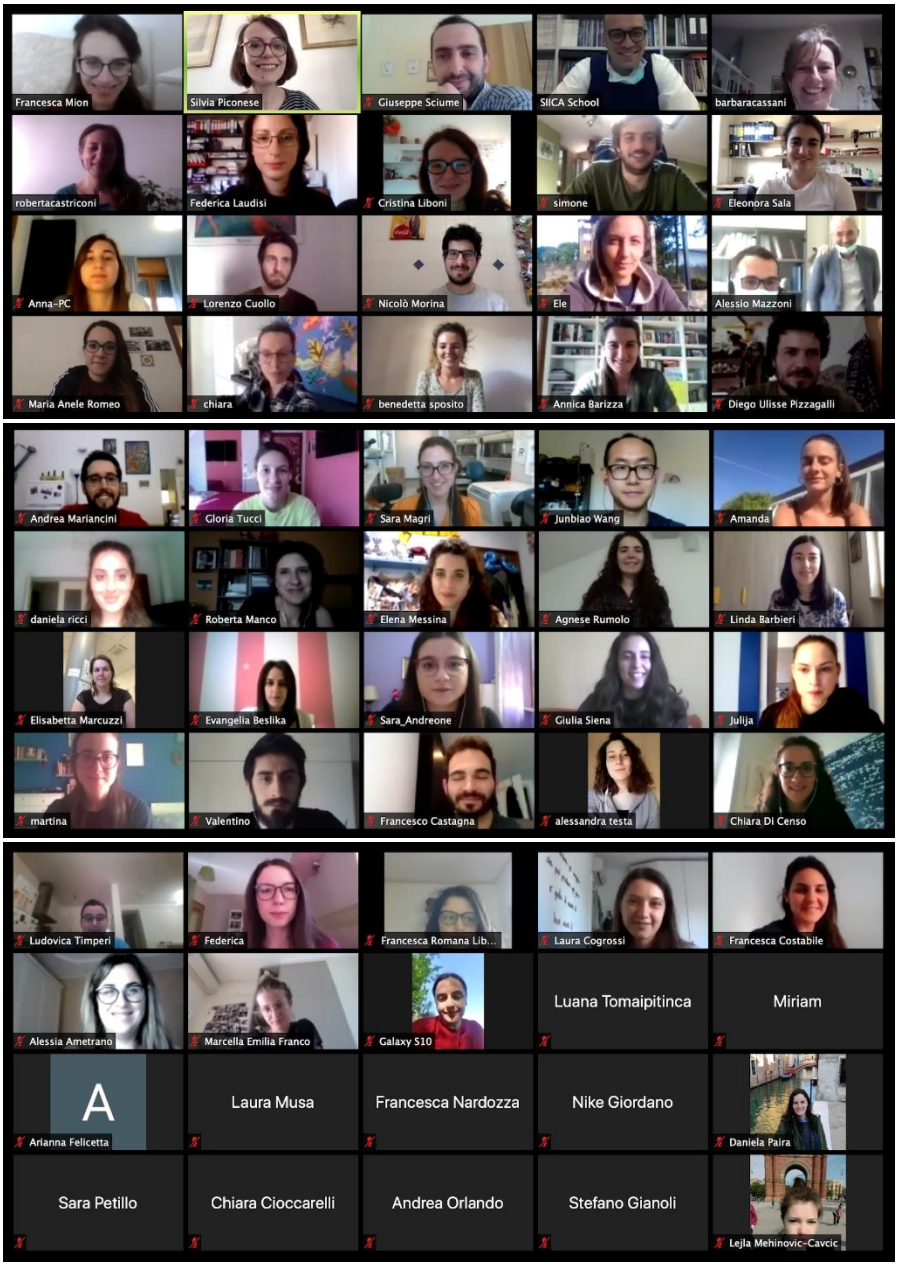
And it was in this climate of uncertainty that the SIICA and the SIICA JF thought of doing something concrete and organized a School on the topic of "Viral Immunology and Vaccinology" that had the purpose not only of occupying our days but, above all, of teaching us something regarding an immunology field that sometimes does not get the attention it deserves.

The success of this school would not have been possible without the valuable contribution of our speakers and our sponsor, but we should especially thank the students who actively participated in this initiative, breaking down the distances that divided us.

This "Task assignment collection" collects the reasoning and consequent answers that students have proposed in response to interesting open questions raised by our speakers during the School, and would like to be a thank that the organizers want to do to those who rendered this school a special event.

SIICA

SIICA Junior Faculty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Nike Giordano
Daniela Paira
Sara Petillo
Chiara Cioccarelli
Andrea Orlando
Stefano Gianoli
Lejla Mehinovic-Cavcic

Summary

Chapter 1

Difficulties and challenges for preventative HIV and SARS vaccines: which will be first, and will it/they confer a durable immunity?

Prof. Guido Poli and Dr. Elisa Vicenzi

The cancer immunology students

Sara Magri, Andrea Mariancini and Benedetta Mattorre

We think that SARS vaccine will come before the HIV one because the outbreak of SARS-COV-2 represents at the moment a pressing emergency worldwide and many scientists have now received funding to find a vaccine. To date, also an Italian company will start a clinical trial for a possible vaccine. Anyway, it will be very challenging because actually our knowledge of the immune system reaction and virus evolution is still restricted. We need to study in deep the evolution of the serological response in recovered patients to understand if a long-lasting immunological memory is developed.

The Anti-bodies

Elisabetta Marcuzzi, Andrea Uva, Ludovica Timperi and Valentina Orticelli

From our point of view, SARS-CoV2 vaccine will be developed first. This since HIV transmission can be easily prevented through behavioral precautions, clinical trials did not find an effective vaccine so far and lastly because many efforts are being put in SARS-CoV2 research due to the recent pandemic emergency. Regarding the acquisition of a durable immunity, we think that since RNA viruses have a high frequency of mutations, antigens may change frequently, thus impairing the lasting of the protection of the vaccine for a long period of time.

Vaccines discovery

Parul Chandorkar, Maria Giovanna Ciliberti and Bianca Partini

It is more difficult to find out a good vaccine for HIV infection rather than SARS virus. Major difficulties are linked to the long-lasting duration of HIV incubation

(10 years) compared to SARS (1-2 weeks) incubation. Moreover, at the moment, we still do not have clinical data of spontaneous resolution of HIV infection. In order to obtain a durable effect, the challenge of using monoclonal antibodies from healed patients can be strategical for obtaining a durable immunity in both diseases.

Vaccine

Matteo Gallazzi, Francesca Biscu, Daniela Paira, Hoang Oanh Nguyen and Mariantonia Braile

Considering the on-going pandemic in the world, we recommend a vaccine for SARS, preferably inactivated by heat given the speed in developing it and the convenience of a single injection. Once the emergency returned, a recombinant protein vaccine, which is safer, could be suggested. The immunity will last for a maximum of a year, hopefully enough to develop a long-lasting recombinant protein vaccine against virus spikes. We suggested the nasal route due to a large amount of organized immune system cells in the mucosa, high absorption and well vascularized surface, fast absorption, rapid onset of the effect and good bioavailability.

Lab Bats

Chiara Dal Secco, Laura Grassi, Alice Masserdotti, Anna Pasotti, Giulia Siena and Rachele Di Donato

Probably SARS-CoV-2 vaccine will come first, because of emergency and government funding. Furthermore, without a model for natural immunity, it would be challenging to identify an immune response that would be effective against HIV, and thus developing an HIV vaccine is difficult. Nowadays researchers have not enough information about SARS-CoV-2 immunity and the possibility of a re-infection. Eventually, scientists should focus on patient's rehabilitation in order to understand if they have developed an immune response (neutralizing antibodies) that can protect them from a second infection in order to have an idea of the effectiveness of a possible SARS-CoV-2 vaccine.

Interferons

Anna Rigatelli, Ludovica Di Martino, Gianluca Scarno and Francesco Castagna

Our group reckons a SARS vaccine would be developed sooner than an HIV one as: the broader spectrum of hosts for the coronavirus makes it easier to study; SARS patients can reach a natural spontaneous remission while HIV ones cannot; only few disease-causing coronavirus strains detected so far while HIV strains are many. A durable immunity would be conferred by a SARS vaccine, given its slower mutational rate at genomic level and incapability to latency compared to HIV. Also, promising long-lasting neutralizing antibodies have been found in SARS-CoV patients able to cross-neutralize SARS-CoV2 *in vitro*.

Happy Quarantines

Daniele Sarnello, Gloria Tucci and Benedetta Sposito

The unsuccessful outcome of HIV vaccines is due to its latency and high mutation rate of the Env protein, which leads to an ineffective antibody response. Conversely, during attempts to develop a vaccine against SARS-CoV and MERS-CoV, the Spike protein has been shown to be a stable and promising target, suggesting that a similar approach for SARS-CoV-2 vaccine production might be fast and effective. Since in SARS-CoV recovered subjects memory T cells persist for longer than specific-IgG antibodies, we think that vaccine strategies eliciting both cellular and humoral immunity would confer the most durable protection.

PAN-SIICA

Giorgia Paldino, Alessia Ametrano and Francesca Nardozza

The first vaccine that will be used on population will be the one against SARS-Cov-2: although HIV has been studied for many years, there are therapies that can keep the infection at bay, also the way to transmit is easier to monitor than SARS-Cov-2. Escape of viruses, the rate of mutations and the relationship with the immune system are just some of the difficulties in creating vaccine. The global healthy emergency maybe will lead scientists to create a vaccine with a durable immunity strengthening the innate immunity by the concept of trained immunity, to have stronger B and T responses.

AFA

Agnese Rumolo, Arianna Felicetta and Francesca Montenegro

A preventive vaccine for SARS-CoV-2 is likely to be available earlier than that for HIV. Indeed, HIV displays important differences compared to SARS-CoV-2 that allow it to escape from vaccines: it is a retrovirus able to integrate into the host genome, it has an extremely high mutation rate, it has CD4+ lymphocytes as target cells and its latency may last for years. More importantly, there are no reported cases of acquired immunity for HIV. The higher stability of SARS-CoV2 genome and the numerous cases of resolved infection through the host immune response are promising features for a preventative vaccine breakthrough.

WeAreViral

Magdalini Alexandridi, Julija Mazej, Mariavittoria Laezza, Simone Marcella, Miriam Capra and Francesca Pettinella

Some encouraging results about Spike protein selection will bring us to the SARS-Cov2 vaccine, even if safety tests must prove its effectiveness profile. A recombinant protein vaccine could be the best solution, since we have to resolve the problems of a good balance between antibodies and T-cell-mediated-response and the absence of co-morbidity. In a comparing way, mutability of HIV virus has made its study difficult, making antiretroviral drugs composition simpler than vaccine production. Immunity induced by SARS-Cov2 vaccine should last for a year, considering first molecules very favorable, despite their partial immunological properties, and could be administered in nasal mucosa, optimizing its absorption.

Quaranteam

Alessandra Testa, Uxía Alonso, Antonino Lo Cascio, Daniel Garzon and Dario Cardamone

Finding a vaccine for HIV is a challenging task yet to be accomplished. The virus's high rate of mutation allows it to keep on eluding the immune response by slight changes of epitopes. Coronaviruses have lower mutation rates, therefore the effectiveness of future vaccines will be more prolonged, as suggested by the finding of antibodies capable of cross-targeting different coronaviruses. Thus, developing a vaccine for SARS-COV2 is more feasible than for HIV. However,

some questions remain to be answered which will impact the design of a vaccine, e.g. the durability of the memory generated, the role of antibody isotypes.

Pizzagalli-Duran

Diego Ulisse Pizzagalli and Ileana Duran Fernandez

SARS virus does not enter the nucleus for replication, and it has proofreading mechanisms which protect it from mutagenesis. In contrast, HIV has an extremely high mutation rate because of error-prone reverse transcription, and it inserts into the host cell genome to replicate. This yields us to speculate that a vaccine against SARS, with a durable immunity, could be easier and faster to achieve than to HIV. Moreover, because HIV attacks directly the immune system, the durability of immunization will depend on the balance between the rate of the memory response and the damage induced by the infection.

ITARIAN

Eleonora Sala, Francesca Costabile, Leila Mohammadnezhad and Mojtaba Shekarkar azgomi

The most important difficulty to overcome for an effective preventive HIV vaccine, is that antibodies are unable to clear HIV infection, since HIV bnAbs have a high number of mutations. At the moment, in our opinion, the best candidate could be anti-tat protein which elicits specific humoral responses and shows a long-lasting stabilization of CD4+ T-cells. Regarding Sars-coV, an hypothetical vaccine might be ineffective in elders due to immune senescence. Moreover, there are not evidences yet about coronavirus long lasting immunity. CD8+ T memory cell epitope-specific immunization might be an alternative and more rapid way than HIV specific immunization. the most important problem in HIV infection, is the downregulation of MHC I molecules which still cannot be seen in SARS-CoV-2, So, due to such problems in HIV- vaccines, the discovery of an earlier vaccine for SARS-CoV-2 respect to HIV comes to mind.

Room14 communication

Marcella Franco, Andrea Orlando, Nike Giordano, Sara Petillo and Luca Mezzanzanica

Considering the pandemic, we are currently living and the consequent immense need for a SARS-CoV-2 vaccine, we think this will be the first one produced. The

large amount of money and resources invested together with the previous knowledge built on SARS-CoV-1 will certainly accelerate the development of a new vaccine. In addition, the different nature of the two viruses renders the challenge to find a vaccine very different: the HIV high frequency mutation, the formation of a quasispecie into the patient and the absence of known spontaneous clearance cases of the infection are a major difficulty that is not present in SARS-CoV-2. With regard to durability, HIV mutation frequency will always test every vaccine.

The PhanDemics

Evangelia Beslika, Valentino Ribecco, Erica Parisi and Martina Morandi

"Which will be first? The emerging situation brings scientists to focus the attention on Sars-Cov2. After 40 years on HIV research they are still struggling due to its unstable antigenic structure and the absence of patients that did not recover spontaneously. The failure to take into account the biology of HIV quasispecies has prevented the development of a better approach. Differently Sars-CoV2 has many characteristics in common with Sars-CoV and Mers, as well as other animal coronaviruses of which we possess vaccines and in-depth knowledge that would allow us to obtain a vaccine ""more easily"" without forgetting that research takes time.

“Will it/they confer a durable immunity?” Several data over the years about Sars-CoV, confirmed that Sars-CoV-specific antibodies were maintained for an average of 2 years. Thus, taking into account that Sars-CoV and Sars-CoV2 share a considerable amount of their genetic material, we are in a situation somewhere between chickenpox infection, where the infection confers almost universal and long-lasting resistance, and seasonal coronaviruses (such as those that cause common colds), for example, that start to decrease a couple of weeks after infection. Hence, the presence of antibodies to the SARS-CoV-2 virus could provide some protection, but more data are needed to determine how long the immunity lasts.

Breakout room 4

Amanda Facoetti, Federica Farina, Eleonora Martinis and Luana Tomaipitinca

The vaccine for SARS-CoV-2 will be the first one to be developed. Its rate of expansion is much faster than other coronaviruses, leading to a global issue pandemic. This makes the vaccine a priority over the one for HIV, as many effective therapies (CAR-T) allow to treat HIV-infected patients and to guarantee them a good quality of life. Although coronaviruses generally tend to mutate less than other viruses due to their efficient error correction system, anti-SARS-CoV-2 vaccines will probably not confer lasting immunity because the virus has just made the leap and therefore it can be considered instable.

Breakroom 12

Nicolò Morina, Valentina Casella, Anna Vanni and Francesco Gasperoni

Although the development of a vaccine for SARS-CoV2 is just a matter of time, the challenges for an HIV vaccine are much higher. While SARS-CoV2 has a stable genome and its transmission routes are clinically more studied, HIV's high mutation rate and early latency establishment, together with lack of clear immune correlates of protection and animal models, represent big obstacles. Moreover, given the huge threat that SARS-CoV2 represents both for health system and economy, the global efforts to counteract its spread are enormous. Ongoing studies suggests that vaccines for SARS-CoV2 may guarantee durable immunity, unlike HIV, given its mutability and low and late immune response.

The quarantine girls

Cristina Liboni, Sara Andreone, Chiara Cioccarelli and Federica Lucini

In our opinion the first vaccine produced will be the one against the SarsCov-2 because its spread is more difficult to control and more studies about other viruses of the same family are already available. Preliminary works on SarsCov-1 and Mers demonstrate that vaccines elicit an effective immune response. Furthermore, evidences on SarsCov-2 patients show a natural ability to clear the infection, while this is not true for HIV patients. Since patients recovering from SarsCov-1 and Mers showed neutralizing Abs persistence until two years after infection, we think that the vaccine might give a similar protection.

Chapter 2

Are there lessons to be learned from dengue immunopathogenesis that can be applied to the current Covid-19 pandemic with regards to therapeutics and/or vaccine development?

Prof. John Hiscott

InVaccineWeTrust

Ludovica Timperi, Andrea Mariancini, Annica Barizza and Francisca Venegas

The scientific community is focused on the generation of neutralizing antibodies and on the development of a vaccine against the emergent Covid-19 disease. Due to the lack of knowledge regarding SARS-Cov-2 immunopathogenesis, it is advisable to exploit the knowledge we have on better characterized viruses. One of the emerging aspects of COVID-19 is the cytokine storm syndrome. This phenomenon was previously characterized in Dengue virus, in which it is due to the antibody dependent enhancement (ADE). Both these aspects should be taken into consideration in order to develop an effective vaccine and/or possible therapeutic treatments.

Ladies of Dengue

Agnese Rumolo, Alessia Ametrano, Uxía Alonso and Daniela Ricci

Host innate immune response plays a crucial role in blocking viral replication. Since Sars-CoV-2 may suppress I-IFN pathway, a possible therapeutic approach could be up regulating I-IFN production to interrupt viral replication in infected cells and prevent it in uninfected cells. Another approach could be down regulating Sars-CoV-2 induced cytokine storm. Sars-CoV-2 has two serotypes and, therefore, ADE cannot be excluded. However, engineered bispecific antibodies, with each Fab structured for a specific target (for example, the Spike protein and ACE2 receptor) may be the key to both prevent this phenomenon and stop viral entry.

FcGamma

Beatrice Ludovica Ritondo, Laura Cogrossi, Cristina Liboni and Ileana Duran Fernandez

Dengue virus and Coronavirus share Antibody dependent Enhancement (ADE), a phenomenon in which antibodies (Abs) targeting one serotype of the virus, only subneutralize another during a secondary infection. Indeed, heterotypic Abs-viral particles complexes are recognized by FcɣR receptors on immune cells and facilitate viral entry, inducing a cytokine storm which accounts for disease severity. Because of this, ADE should be a primary concern to take into account in the design of a vaccine. Following Dengue experience, the vaccine against SARS-CoV-2 should either block all coronavirus serotypes or target an epitope unique to SARS-CoV-2, in order to avoid ADE.

The Sunday Night Fever

Elena Messina, Bianca Laura Cinicola, Alice Masserdotti and Linda Barbieri

Different approaches to fight Covid-19 can arise from the knowledge of Dengue immune-pathogenesis. Like in DENV, the main evasion mechanism of SARS-CoV-2 seems to target the IFN-I response, so a promising strategy could be act against proteases that cleaves STING or MAVS. Moreover, the severity of DENV and SARS-CoV-2 infection could be related to the aberrant adaptive immune response expressed as ADE and cytokine storm. Considering that, several interventions could be proposed such as key pro-inflammatory cytokine antagonists and host modulators. Finally, since DENV vaccine can lead to the exacerbation of infection following ADE, the characterization of these mechanism is critical to avoid the same process in the current pandemia.

SPIKE's girls

Chiara Dal Secco, Rachele Di Donato, Sharon Eleuteri and Anna Vanni

The timing to realize SARS-CoV-2 vaccine cannot be reduced and further studies are needed due to the complexity of the pathways involved in the immune response. Dengvaxia vaccine failure is an example of ADE phenomenon's underestimation. It is not known if different SARS-CoV-2 serotypes have already developed, but there are studies focused on the likelihood of ADE by linking neutralizing antibody and the spike protein to mediate not only viral entry in Fcγ receptor-expressing cells, but also to interfere with important pathways involved

in IFN-1 production. Restoring the balance of this pathway of innate immunity, could be a therapeutic strategy exploiting molecules studied for dengue virus, considering that are both enveloped ssRNA virus. In this context, it should be considered that there are different clinical courses and in case of more severe cases it will be necessary to develop alternative therapies to avoid the worsening of patient's condition.

Phinding coviD

Anne Lise Ferrara, Federica Farina, Erica Parisi, Chiara Cioccarelli and Hoang Oanh Nguyen

The immunopathogenesis of dengue virus is not fully understood. However, it has been reported that antibody dependent enhancement (ADE) and oxidative stress are associated with the development of inflammation and progression of severe forms of dengue. Therefore, it is interesting to see if ADE also contributes to the pathogenesis of SAR-CoV-2 and if SARS-CoV-2 is able to infect macrophages as dengue in order to develop an effective vaccine. Additionally, investigating the ROS in SARS-CoV-2 could also give us information about the relationship between oxidative stress and the immunopathogenesis of the virus in order to find key factors useful for therapies to reduce virus replication.

De(li)ngue(nts)

Francesca Costabile, Luisa Loconte, Fabiola Vacca and Matteo Gallazzi

Like the Dengue virus, Sars-CoV-2 might encode for the NS-proteins which allow the Dengue virus to shut down the innate antiviral immune response. In a therapeutics scenario of Sars-CoV-2, it might be useful to discover the common features with Dengue virus and the possible inhibition of pathological symptoms by targeting the NS-proteins. The Antibody Dependent Enhancement event, confirmed in the Dengue pathology, should let us suppose that Sars-CoV-2 patients present non-neutralizing Abs, leading to poor prognosis; however, good outcome may occur by blocking the binding with the Fc receptor in this case. As anti-prM antibodies against DENV, a COVID-19 vaccine candidate should be designed in a way to minimize the antibody immune response to components that elicit ADE. The fortunate match of all the above features led us speculate that the modification of an already approved vaccine against RNA virus, e.g. Dengvaxia

vaccine, could be a valid alternative for the Sars-CoV-2 vaccination, providing its safety before.

ADE-Haters

Sara Andreone, Benedetta Sposito, Laura Musa, Evangelia Beslika and Prisca Mauro

It is critical to avoid vaccine-induced enhancement of infection. ChimeriVax-DEN-2 induces ADE in seronegative patients instead Dengue specific live attenuated vaccines like TV003 do not. Regarding SARS-CoV vaccines tested in animals some of them do induce it, while others like inactivated SARS-CoV Z-1 vaccine do not. Thus, developing either a live attenuated or an inactivated vaccine against SARS-CoV-2 could be a good strategy to escape ADE, as well as to elicit a T-cell response. Alternatively, production of Abs against non-neutralizing epitopes of the S protein could be avoided by glycosylating them or by immunofocusing on the RBD.

Viralicious

Magdalini Alexandridi, Simone Marcella, Martina Morandi, Laura Grassi and Andrea Uva

The possibility of developing ADE, caused by reinfection by a Dengue serotype different from the one in the primary infection, is the main reason for the ineffectiveness of the developed vaccine. Three strains of SARS-CoV-2 have been identified and it is unknown if this will impede the vaccine development. Extensive safety tests must prove the effectiveness profile against the possibility of ADE or cell-based enhancement occurrence. Severe forms of Dengue and Covid-19 have been correlated with complement activation, the cytokine storm and oxidative stress. The main focus should be on developing and testing antiviral drugs like inhibitors for the viral polymerases (possibly nucleotide analogs) or viral proteases or targeting host metabolic (TCA cycle, Itaconate), inflammation (IL-6) and redox homeostasis (Nrf2) pathways.

IMMOON 5

Francesca Biscu, Francesca Nardozza, Eleonora Martinis, Francesco Gasperoni and Anna Rigatelli

The greatest lesson learnt from Dengue could be about vaccine: a careful evaluation of possible immune complications is required before releasing the vaccine to the public, especially because immune enhancement can manifest itself in several ways such as ADE and/or Th2 immunopathology. ADE posed a challenge in creating vaccines for infections of Dengue. Anecdotal SARS-CoV2 re-infections could give credit to the relevance of ADE, the production of antibodies against the virus ends up improving entry of the virus into cells. Potentially more serious SARS-CoV2 infections could be caused by Th2 immunopathology. As noted in RSV vaccine, the immune cells of the vaccinated animals attacked lung tissue. The second lesson regards the therapy: the limited knowledge of viruse's pathophysiology does not allow us to focus on a single target. This entails us to enhance the innate immunity and test antiviral therapies previously demonstrated to be effective on other viruses.

Quaranteam 2.0

Sara Magri, Dario Cardamone and Miriam Capra

Antibody-dependent enhancement is a characteristic event that occurs in Dengue Fever and SARS-Cov2 patients after a secondary infection. Chemokines production and T-cell recruitment concur on infection blocking, despite their simultaneous function in vascular permeability increase. In a comparing way, INF release is compromised by STING activity inhibition in SARS-Cov2, countering immune system defensive efforts. An aberrant inflammatory response destabilizes the bio-humoral equilibrium: NfKB regulation through RIG1 and MDA5 modulation could restore an "immunological balancing", improving antivirals and immunomodulators efficacy. Vaccine development should overcome the tricky serotype-dependent variety of SARS-Cov2 virus, obtaining a polyhedral molecule with effective skills in immunogenic microenvironment-control.

Girls Biopower

Amanda Facoetti, Benedetta Mattorre, Gloria Tucci and Maria Anele Romeo

The main problem encountered in the development of the dengue vaccine is that some healthy subjects vaccinated showed exacerbated immune responses after virus infection. Several studies demonstrate that this phenomenon is related to ADE (antibody-dependent enhancement). A major question in Covid-19 pulmonary disease is why a small percentage of patients experience persistent inflammation, and eventually succumb, while other patients survive. Some authors have highlighted a possible role of ADE also in coronavirus infection, to this extend we think that vaccine development will need to take this phenomenon into consideration in order to avoid what happened for the dengue vaccine.

SaturdayDengueFever

Sara Bozzer, Antonino Lo Cascio and Nicolò Morina

DENV and SARS-CoV-2 have both positive-sense ssRNA genomes, suggesting a similar sensing pathway by host cells. Indeed, viral RNA is recognized by RIG-like Receptors, such as RIG-I and MDA5, leading to transcriptional regulation of inflammatory cytokines and Interferon response. Even if SARS-CoV-2 is considered more stable than DENV, both viruses may share the Antibody Dependent Enhancement (ADE) mechanism, promoting viral entry and replication. Indeed, Abs to other Covs may exacerbate COVID-19 disease. Thus, this should be considered for therapy and vaccine development. Moreover, since Itaconate reduces inflammation in Dengue, we hypothesize the use of anti-inflammatory metabolites to decrease tissue damage and cytokine storm contributing to mortality of COVID-19 patients.

Venom-STING

Riccardo Capecchi, Sara Coletta, Elisabetta Marcuzzi, Alessandra Testa and Sara Virtuoso

Our group believes that there are several points in common between SARS-CoV-2 and Dengue virus. SARS-CoV-2 results in a dysregulated host immune response which culminates with a cytokine storm. Likewise, the severity of Dengue disease is widely associated with cytokine-mediated pathology occurring due to its ability to elude the host innate immune response, in agreement with immune-escape observed for other coronavirus strains. Highlighting upstream mechanisms of

cytokine storm as potential therapeutic targets. Moreover, the suggesting possibility that antibodies to one type of coronavirus could enhance infection to another viral strain, recalls the biggest problem found in the development of vaccine against Dengue virus due to the antibody-dependent enhancement (ADE) phenomenon, definitely a lesson to learn.

Dengue vs Covid19

Anna Pasotti, Valentina Orticelli, Roberta Manco and Mariavittoria Laezza

One lesson from Dengue disease could be addressed to the antibody-dependent enhancement (ADE) phenomenon. A first infection with Dengue virus produces protection to one serotype but also some cross-protective immunity against other serotypes. Once the protective antibodies wanes, severe forms of disease can develop in same patients by ADE. Some researcher speculated that, as for Dengue, SARS-Cov-2 virus could also follow the same mechanism leading individuals exposed to heterogenic antigen epitopes to progress into severe stages of secondary infection. Other hypothesis sustain that populations affected by endemic Dengue are less vulnerable to SARS-Cov-2 due to immunological memory. Immunization with Dengue vaccine in non-endemic countries is less likely to show ADE. In any case, ADE phenomenon should be taken into consideration when designing vaccination programs.

ADECesare

Andrea Orlando, Maria Pozzi, Sara Petillo, Giorgia Paldino, Giulia Siena and Diego Ulisse Pizzagalli

Viral infection induces a systemic reaction. Hence, multiple aspects should be considered. About immunopathogenesis, ADE should be investigated because it could enhance viral infection in certain patients. Antibody toxicity also should be considered as can yield to multi-organ failure. SARS-CoV2 infection could promote an high inflammatory response (IFN-I and IL-6 production) and oxidative stress. Hence, cGAS, ALK, STING, NF-kB and metabolic pathways could be potential therapeutic targets: modulate rather than block them could prevent side effects. As C-type lectins can both recognize viruses and be exploited for cell entry, administration of soluble lectins could confer protection by competition. In conclusion, rushing a Sars-CoV-2 vaccine could lead to underestimate risks and long-term effects as taught by the DengVaxia Program.

Na Tazzulell 'e COVID

Mariantonia Braile, Lorenzo Cuollo, Luca Modestino and Michele Tufano

Antibody-Dependent Enhancement (ADE) is involved in the immunopathogenesis of SARS-CoV, leading to ARDS and cytokine storms in individuals that developed or that are treated with IgG against the Spike protein. If ADE will be confirmed for SARS-CoV2, this should be considered when designing vaccines. Furthermore, blocking FcγR receptors during COVID-19 may be beneficial. Upon exposure to inflammatory agents, macrophages are activated and could undergo a metabolic switch producing itaconate, which has powerful anti-inflammatory activity, blocking the release of IL-1 and IL-6, and indirect antiviral activity via Nrf2 pathway. Therefore, itaconate and Nrf2 pathways could represent pharmacological targets to modulate the immune response, preventing cytokine storms.

Hell Storm

Arianna Felicetta, Luana Tomaipitinca, Stefano Gianoli, Francesco Castagna and Gianluca Scarno

DENV and SARS-CoV2 can excessively trigger innate immunity, mostly in terms of cytokine storm and complement activation. However, the contribution of the immune response may follow virus-specific trajectories, since DENV has developed strategies to evade type I IFN activity, while the depletion of IFNAR signaling ameliorates the pulmonary condition in SARS-CoV infection mouse model. The run for developing vaccines must not compete with the safety of the approach, and the presence of several serotypes is critical. Secondary DENV infection can be boosted by ADE; therefore, the effects on different serotypes should be considered also for SARS-CoV2 vaccine development, since neutralization of SARS-CoV2 by antibodies originally directed against SARS-CoV has been observed.

Dengue Rules

Ludovica Di Martino, Nike Giordano, Luca Mezzanzanica and Eleonora Sala

Dengue immunopathogenesis has opened new perspectives to unveil the starting point of COVID-19; developing vaccine could be challenging if suboptimal neutralizing antibodies give rise to "antibody-dependent enhancement". Like

dengue infection, the severity of COVID-19 seems to be correlated with a cytokine storm that suggests a detrimental immune response. New insights on Dengue immunoevasion could suggest, also for COVID-19, a metabolism role in both shutting down a proper antiviral response (e.g. inhibition of IFN signaling) and reducing mortality in the infected cells. If confirmed, this link between metabolism and antiviral activity could pave the way to new therapeutic approaches, that target upstream the IFN cascade.

SCIENTISTSontheCOUCH

Ersilia Vinci, Valentino Ribecco, Daniela Paira and Julija Mazej

As for Dengue, in SARS-CoV-2 infection the increased risk of acute respiratory distress syndrome, myocardial damage, and death has been associated to a cytokine storm, that can be attenuated through inhibitors of JAK1 pathway. Another pathogenic feature common to both, Dengue and SARS-CoV-2 is oxidative stress, which could be reduced with chemical targeting of Nrf2 pathway. Furthermore, inhibitors of viral polymerases, e.g. adenosine analogues, may be developed for SARS-CoV-2, given that its structure of RNA-dependent RNA polymerase was recently published. In Dengue it is vastly demonstrated that high neutralizing antibody titers lead to an increase in viral replication by Antibody-Dependent Enhancement (ADE). In COVID19 infection there are evidences that high titers of specific IgG correlate with a worse prognosis, possibly mediated by ADE. We therefore propose the use of vaccines that stimulate the immune response of specific cytotoxic T-CD8 cells by modulating DC through adjuvants. We exclude the possibility of a live attenuated vaccine (current Dengue vaccine, Dengvaxia), that might be dangerous for people with a weak immune system.

Chapter 3

Which immune mechanism would you like to study to treat SARS-Cov2 infection and immunopathogenesis?

Prof. Andrea Cossarizza

Covid-Fighters

Andrea Orlando, Nike Giordano, Francesca Nardozza, Sara Petillo and Diego Pizzagalli

Considerable efforts have been made to fight the spread and the pathogenicity of SARS-COV2. However, to date there has been no resolutive therapy, due to its incredible ability to hijack on various levels the immune response. Hence, we should probably deepen the study on the entry phase of the virus to block the first stage of its pathogenesis. At this regard, some promising approaches are based on TMPRSS2 inhibitors, nABs, recombinant ACE2 and soluble lectins. Moreover, we consider critical the role of the innate immune response in the early phase of the infection and how this shapes the following adaptive response.

Covidstorm

Francesca Romana Liberati, Andrea Uva, Matteo Gallazzi, Anna Vanni and Hoang Oanh Nguyen

All immune mechanisms involved in Sars-cov-2 infection are attractive fields of study. Hyper-inflammation, a condition characterized by the uncontrolled immune cell activation and cytokine release, has been proposed to drive the severity of Covid-19. Understanding the mechanism that brought to hyperinflammatory phase from the early infection will be useful to prevent the worsening of the disease and also to predict which patient will develop a severe condition. It will be also important to analyze the role of adaptive immunity in Sars-Cov-2 pathogenesis. Immune responses in many patients do not effectively switch from innate to adaptive with little antibody production, but future vaccination strategies will be needed to elicit strong protective antibody responses.

SamSARS

Elisabetta Marcuzzi, Alice Masserdotti, Sara Virtuoso and Junbiao Wang

Endotheliitis induction in several organs is a direct consequence of viral involvement during SARS-CoV-2 infection. Endothelial dysfunction and host inflammatory response, exponentially increase the production of inflammatory cytokines, such as IL-6, IFN, TNF-α, and chemokines. This increase explains the systemic impaired microcirculatory function, characterized by enhance vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and procoagulant state. Additionally, the late stage hyper inflammation, with ARDS and shock as symptoms, may be related with the high pulmonary neutrophils' infiltration and their production of "Neutrophil Extracellular Traps", probably related to mortality. We hypothesize that reduction of the immune inflammation by administration anti-IL 6 and recently speculated anti-IL-17, and the restore of the endothelium integrity by anticoagulant administration, while tackling viral replication, could be a therapeutic strategy. Moreover, the simultaneous limitation of NETs release can be promising for the adjunctive therapy.

Grl(Pwr) on the same pathway

Mariantonia Braile, Chiara Cioccarelli, Maria Anele Romeo, Francisca Venegas and Ersilia Vinci

In SARS-Cov-2 pathogenesis has been shown an increase of neutrophils, with a massive production of IL-6 and TNF-α, and a reduction of lymphocytes. Indeed, patients with severe symptoms present lymphopenia as a common feature, as well as an increase in neutrophil count. Controlling neutrophils activity is crucial and, because IL-17 (secreted by T helper CD4+ cells), recruits and activates neutrophils, we consider the blockage of IL-17 secretion a way to reduce the activation of neutrophils and hence the production of pro-inflammatory cytokines such as IL-6 and TNF-α. This would finally lead to low ROS and NO productions and a reduced damage to alveolar cells, guaranteeing a balance between innate and adaptive immune response.

InflammaVid

Giuseppe Pietropaolo, Valentina Orticelli, Elena Messina and Sara Coletta

Cytokine storming is one of the most frequent complications that occur during the acute phase of Covid-19. Among all cytokines involved, IL-6 and IL-17 have a key role in Covid-19 pathogenesis synergistically promoting pro-inflammatory response, expression of chemokines and neutrophils recruitment. IL-6 and IL-17 can converge on JAK2/STAT3 signaling and, through different ways, on NF-kB activation. Since IL-6, IL-17 and JAK2/STAT3 appear functionally linked in a positive feedback loop, the in depth study of this pathway could be a successful approach, in order to propose a combined therapy hitting multiple players, both upstream and downstream, of the same pathway that may be activated by different stimuli.

SARS e Merengue

Francesca Costabile, Chiara Di Censo, Lorenzo Cuollo and Daniela Ricci

Neutrophils Extracellular Traps are emerging as important factors in host defense; however, they can contribute to clinical manifestations observed in COVID-19, such as ARDS, microthrombosis and cytokine storm. The detrimental effect of excessive NETs formation is particularly important in lung disease, though it is not clear whether they represent causes or consequences of dysregulated immune response. It is hypothesized that NETs are implied in COVID-19 immunopathology, since neutrophil infiltration was observed in lung autoptic samples. If their implication will be proved, therapies targeting NETs formation/stability or neutrophils proliferation/recruitment could show positive results. Such therapies may also provide benefit for other disorders in which NETs are involved.

Thunderstorm

Francesca Biscu, Arianna Felicetta, Simone Frascolla and Maria Pozzi

Innate immunity plays a crucial role in protective or destructive responses against SARS-CoV-2 and may open new windows for immune interventions. Surprisingly, flagellin seems to help innate immunity activation via TLR5, inducing the production of IFN-β and IL-22. Moreover, active viral replication results in hyper-production of type I IFN and influx of neutrophils and macrophages, the major

sources of pro-inflammatory cytokines, leading to the loss of viral control in the early infection phase. Therefore, both MAS-like lung inflammation and NETs trigger pulmonary vascular disease, prompting to unfortunate outcomes. Since the early inflammation phase is a key aspect for the pathology, and due to the intense crosstalk between the mentioned mechanisms and the cytokine storm, we think that these processes should be better clarified in order to exploit them in the development of new personalized therapeutic approaches.

Viral Rhapsody

Anna Pasotti, Cristina Liboni, Mariavittoria Laezza, Simone Marcella, Ludovica Timperi, Flavia Trionfetti and Julija Mazej

Covid-19 is characterized by pulmonary inflammation associated with increased plasma levels of pro-inflammatory cytokines, a phenomenon described as cytokine storm. If not mitigated, this phenomenon leads to an acute respiratory distress syndrome (ARDS) and death. Therefore, it is vital to weaken the hyper-inflammatory state by using neutralizing compounds but, at the same time avoiding a broad immune suppression. Th17 contributes to the cytokine storm and promotes neutrophils recruitment in the lungs. Addressing TH17 cells represents a promising strategy to improve disease outcome. Targeting JAK2, a downstream signaling protein in TH17 activation, blunts IL17 and IL22 release *in vitro* and furthermore, reduces IL6 and GM-CSF, ROS and NOS production. Acting on TH17 could also restore the TH17/Tregs ratio, which is considered a positive prognostic marker for ARDS.

Thrombi-enemies

Benedetta Sposito, Valentino Ribecco, Antonino Lo Cascio, Benedetta Mattorre, Andrea Mariancini and Amanda Facoetti

Hospitalized COVID-19 patients are characterized by an overreaction of the immune system, known as cytokine storm. This hyperinflammatory state determines local and systemic consequences, including pulmonary coagulopathy, that leads to permanent lung lesions. In these subjects a progressive alteration of various coagulation parameters has been observed. Low molecular weight heparin at prophylactic dose should be considered in patients with markedly elevated D-dimers. Several publications have demonstrated anti-inflammatory functions of heparin, such as binding to inflammatory cytokines, inhibiting

neutrophil chemotaxis (possibly preventing NETs formation) and leukocyte migration. We suggest that further investigating the link between the coagulation system and hyperinflammation in COVID-19 immunopathogenesis could improve the development of new therapeutic strategies.

Quaranteam v.3

Fabiola Vacca, Dario Cardamone and Erica Parisi

Viral replication, in SARS-COV-2, triggers elevated inflammatory conditions which may lead to the production of pro-inflammatory cytokines, that can be reduced by using IL-6, IL-2 inhibitors. In parallel to strategies to regulate the inflammatory response, it would be interesting to study the adaptive immune system, such as the B cell response to the virus, both in the short-and long-term. For instance, the virus can be neutralized by antibodies that are capable of recognizing viral surface proteins and inhibit viral invasion of cells. In case of clinical samples, understand the correlation between the antibody titers/kinetics with the clinical status of the patient and investigate how antibodies may correlate to the patient recovery. Overall, we suggest investigating the early phase of the infection, to avoid hyperinflammation and the appearance of severe symptoms, and a later phase as well, to determine if antibodies may play a crucial role in antiviral defense.

STRESS-CoV-2

Sharon Eleuteri, Eleonora Martinis, Evangelia Beslika and Chiara Dal Secco

Since the emergence of the symptoms is delayed over time compared to time of infection, finding the right time to treat the symptoms is crucial. Silencing of INF-I producing pathways is a well-known way of immune escape of SARS-CoV-2. As already seen in SARS and MERS infections, this leads to an insufficient and aberrant activation of the immune response. So, in the first phase of infection, some INF-I pathway enhancers should be used, in order to boost the immune reaction. In a second phase, in order to prevent the cytokine storm, therapeutic approaches that block pro-inflammatory cytokines (or their receptors) are needed; for example, Tocilizumab directed against IL-6 receptors showed inspiring clinical results, and studies on blocking IL-17 pathways seems to have promising applications. This is considered an additional strategy since IL-17 dramatically increases inflammation and activates neutrophils, causing excessive NET formation and associated problems. Lastly, a systematic comparison between

asymptomatic and symptomatic patients is crucial to better understand SARS-CoV-2 immunopathogenesis.

HLA Power

Gloria Tucci, Federica Farina, Miriam Capra, Laura Musa and Sara Bozzer

The understanding of antigen presentation of SARS-CoV-2 will help our comprehension of COVID-19 pathogenesis. While the virus enters the cells, its antigen will be presented to the antigen presentation cells (APC) such as macrophages, dendritic cells and B lymphocytes. Antigenic peptides are then recognized by virus-specific cytotoxic and T helper lymphocytes and the body's humoral and cellular immunity is subsequently stimulated. It could be interesting to study whether specific HLA loci are associated with the development of anti-SARS-CoV-2 immunity and, if so, to identify the alleles, either class I or II, that demonstrate induction of protective immunity in order to consider that in clinical management and in the evaluation of the efficacy of vaccine.

ACEgirls

Roberta Manco, Alessia Ametrano, Giulia Siena, Daniela Paira, Arianna Pastore and Laura Grassi

SARS-CoV-2 seems to delay IFN-1 response and induce loss of viral control in an early phase of infection. Stopping the virus entrance could decrease viral replication and expulsion. The soluble recombinant human ACE2 is expected to prevent the SARS-CoV-2 entrance by blocking the Spike protein. Moreover, by improving engineered inhibitors, it could be possible to simultaneously target different epitopes on the envelope and limit escape pathways by binding its conserved sites (e.g. bispecific and antibody-like inhibitors). Finally, the use of L-asparaginase could prevent the virus-host cell binding since the last amino acid of ACE2 receptors for Sars-CoV-2 is asparagine.

ImmuNETwork

Beatrice Ludovica Ritondo, Luana Tomaipitinca and Annica Barizza

It is crucial to focus on factors leading to the uncontrolled host immune response to SARS-CoV-2 contributing to the severe disease outcome. It was demonstrated in SARS-CoV that delayed expression of IFN-I triggers an inappropriate

inflammatory response during infection, including the accumulation of inflammatory monocytes/macrophages in the lungs. It would be interesting to investigate this mechanism in SARS-CoV-2 to characterize, and possibly control, the early phases of the infection. Furthermore, it would be intriguing to deeper investigate the association between the severity of the disease and the excessive formation of neutrophil extracellular traps (NETs) observed in hospitalized patients, who usually are already in the pulmonary phase. NETs are likely to participate in a strong proinflammatory loop resulting in IL-6 upregulation, therefore key enzymes in formation of NETs show potential as therapeutic targets.

Social NETwork

Sara Magri, Prisca Mauro, Alessandra Testa and Francesca Albano

As it was reported that in severe cases of SARS-COV2 infection there is a high count of neutrophils and that neutrophil-to-lymphocyte ratio (NLR) is a predictive marker of severe development, we are interested in the neutrophil activation pathway. Neutrophils are responsible for alveolar cell damage in lungs, through their ability to produce ROS and NETs. NETs have been shown to play a vital role in initiating and accreting thrombosis. Moreover, NETs can induce macrophages to secrete IL1β and this IL1β enhances NET formation. Therefore, a promising strategy in order to counteract the pulmonary damage could be to prevent neutrophil hyperactivation and NETs formation by controlling the cytokines release, with approved drugs against IL1β. Thus, we believe that targeting NETs with existing drugs may reduce the clinical severity of COVID-19.

I Neutrofiki iNETti

Luca Mezzanzanica, Laura Cogrossi, Rachele Di Donato and Stefano Gianoli

Recent evidences in COVID-19 show that the neutrophils-macrophages axis represents a crucial mechanism of antiviral response, discriminating between the resolution or the worsening of the disease. Pulmonary neutrophilia is a common clinical feature of those patients, and a high concentration of NETs has been reported. Although NETs are usually helpful in the host defense against pathogens, in COVID-19 they can be a double-edged sword. Indeed, an excessive NETs formation can act in synergy with macrophages to sustain cytokine release, leading to hyperinflammation, followed by localized lung damage and micro-thrombosis. This latter, if amplified, may be responsible for systemic organ failure

and death. To enhance the clearance of NETs-induced obstruction, the use of a DNase-I treatment could be a new therapeutic approach during SARS-CoV-2 infection.

SpyTheNet

Linda Barbieri, Bianca Laura Cinicola and Riccardo Capecchi

Older population is badly hit by Sars-Cov-2, with high morbidity and mortality rate. Thus, we postulate that immunosenescence could explain this worse outcome. Since innate immunity represents the first response against infections, we would concentrate on its senescence. We would focus on monocytes, since it was already shown a large increase of CD14+ CD16+ monocytes in noninfected older subjects. Moreover, monocytes are major producers of IL-1β, that is increased in COVID-19 patients and is implied also in NETs formation which stimulates many disease processes during viral infections. Thus, IL-1 family expression in monocytes and in peripheral blood, related to NET formation, could suggest target therapy in COVID-19 patients.

Medicina 33

Anna Rigatelli, Martina Morandi, Ludovica Di Martino, Francesco Castagna and Gianluca Scarno

More evidences are piling up pointing out the central role of both lung-resident and non-resident innate immune players starting and sustaining the severe inflammation in SARS-CoV2 patients. Early signals implicated in initiating type 2 lung inflammation include IL-33. This alarmin, mainly produced by epithelial and alveolar cells, strongly triggers cytokine production by ILC2 (including IL-6) within hours upon infection. Circulating Ly6C(high) monocytes have already been described to migrate to the lung via CCL2/7-CCR2 axis in an IL-33 dependent manner, differentiating into proinflammatory macrophages. Blocking IL-33 by monoclonal antibodies pathway is currently under clinical trial for inflammatory diseases, including asthma. Hence, we hypothesize that its blockage may have positive consequences to the immunopathogenesis associated to SARS-CoV2 infection, acting at two key distinct levels.

MASK FORCE

Marcella Franco, Francesco Gasperoni, Sara Andreone and Nicolò Morina

TRANSMISSION Two open questions regarding SARS-CoV2 virus that need to be addressed by future research are its transmission pathways and its initial onset. The results of such studies may better coordinate social behaviors and refine preventive measures. CLINICAL LATENCY Current evidences have shown a long period of incubation, in which the virus is able to hide from the immune system: this crypto-critical phase, both for the molecular mechanisms and the potential contagiousness of infected people, may be targeted by making the virus visible to the immune system. Thus, the intense immune reaction and the cytokine storm typical of the late phase could be avoided. HYPERINFLAMMATION PHASE There are clues about potential additional tissue targets of the virus (e.g. brain, liver, gut): a complete knowledge about them would be helpful for the development of targeted therapies.

Chapter 4

How can we exploit knowledge of immunoevasins in designing "better" viruses or using such viruses as tools?

Prof. Stipan Jonjic

COVIDeo killed the radio SARS

Alessandra Testa, Cristina Liboni and Francesco Gasperoni

mCMV' and hCMV' immunoevasins interfere with MHC class I pathway, thus avoiding the NK response. Ly49H expressed by NK seems to be the key mediator and its lack triggers a more efficient NK anti-viral response. Furthermore, Ly49H accounts for the development of NK memory cells, bystanders for development of an efficient T/B cells-based response in a secondary infection. The precious knowledge about NK-linked immune evasion strategies employed by viruses like CMV, could be used to improve efficacy of viral vectors used as vaccines against pathogens and cancer. For example, deletion of immunoevasin genes in HCMV-based therapeutic vaccines, coupled with insertion of activating NK-ligands, leads to an increased immunostimulatory activity of the vectors against the antigen/epitope of interest, bursting an important cellular response against cancer.

CorMejoVirus

Luana Tomaipitinca, Sara Virtuoso, Mariavittoria Laezza, Ersilia Vinci and Francesca Biscu

Cytomegaloviruses (CMVs) are expert immune-evaders encoding proteins and microRNAs which interfere with the host immune system. CMVs use immune-evasion strategies to control missing self-dependent NK cells activation through MHC-I molecules regulation. Nowadays, the ability of both CMVs and vaccines to target the immune response, and not tumors directly, is particularly valuable because it is independent from tumor-associated mutations within immune stimulatory pathways. Indeed, murine CMV (MCMV) was proposed to play a role in cancer development and it was studied as a cancer vaccine vector stimulating the STING pathway or acting in synergy with anti-PD-L1 therapy into melanomas to promote anti-tumor immune responses. Exploiting pathogens as tools is an

exciting new strategy to modulate the tumor milieu i.e. recruiting populations of CD8+ T-cells or infecting Tumor-Associated Macrophages (TAMs), which might decrease macrophages production of proangiogenic factors.

I got you!

Maria Pozzi, Anna Vanni, Daniela Ricci, Martina Morandi and Hoang Oanh Nguyen

One great challenge for new virus-based tools will be to control the ability to regulate the immune system. Reverse genetics using BAC mutagenesis can be used to prevent immunoevasins. Single amino acid substitutions at either TCR or MHC-I contact sites of an antigenic peptide can be used to modulate the antigenicity and immunogenicity of an epitope. Such mutations can have an influence on the CD8 T-cell response with a minimal influence on protein function and viral biology. Deleting one or more epitopes functionally by loss-of-presentation point mutagenesis replacing the respective C-terminal "anchor" amino acid residue, involved in the binding of the peptide-presenting MHC-I molecule, could be a promising strategy. Therefore, this type of replacement also impacts its generation by proteasomal cleavage. Consequently, a complete block of endogenous pMHC formation, and thus of peptide presentation in infected cells, can result from the combination of inefficient proteasomal cleavage and low affinity of MHC-I binding.

Escape from immunity

Linda Barbieri, Dario Cardamone, Francesca Costabile, Sharon Eleuteri and Giorgia Paldino

In order to design a "better" virus we can act on immunoevasins, for example deleting genes to identify specific RNA sequences required for evading immune recognition or inserting synonyms mutations which have an impact on chromatin organization and then on genes expression. In this way, we can generate a new type of attenuated vaccine candidates avoiding side effects. These molecules also allowed to investigate the MHC I antigen presentation and less known mechanisms such as PLC-independent antigen presentation pathway and cross-presentation of exogenous protein. Finally, immunoevasins could be exploited in cancer gene therapy (e.g. applications of in cis-acting immunoevasins for the protection of transgenes from the immune system) as they allow specific manipulation of the immune system.

Escape Room

Riccardo Capecchi, Chiara Cioccarelli, Francisca Venegas, Laura Musa, Roberta Manco, Sara Coletta and Sara Petillo

Viral vector-based drugs are already approved for specific gene therapies. However, the host immune response can vanish this therapeutic approach, leading to immunotoxicity, with reduced rate of successful gene replacement, high risk for the patient and need for immunosuppression. A strategy to improve these therapies would be to use viral immune evasion to fix critical immune responses against already approved viral vectors, such as adenovirus, AAV or lentivirus. For example, CMV based m04/m157 proteins could modulate MHC I expression in AAV therapy, susceptible to CD8+ T response. Moreover, other viral proteins, such as measle V protein or influenza NS1 protein, can modulate MDA5/RIG-I activation or inhibit STING in lentivirus *ex vivo* treatments.

H-indeXision

Eleonora Sala, Miriam Capra, Elisabetta Marcuzzi, Sara Andreone, Stefano Gianoli, Evangelia Beslika and Giuseppe Pietropaolo

Immunoevasins are viral glycoproteins that play a fundamental role in shaping the immune system response and in preventing the antigen processing and presentation. These proteins are still not well characterized, however starting from crystallization and X-ray analysis it could be possible to study not only the binding site but also the interactome. Moreover, a mindful analysis of the host –genetic background changes is necessary to understand the mechanisms that the virus carries out to overcome immune defenses and to take advantage paradoxically from them. The lab virus employment is a border already crossed by Clinical Research and can engage many functions, like pharmacological molecules engineering and vaccine realization.

Virius Black

Anna Rigatelli, Eleonora Martinis, Chiara Dal Secco, Simone Marcella and Gianluca Scarno

Although great progress has been made in uncovering the identity and function of immunoevasins, many putative genes remain uncharacterized, and most of the known mechanisms are restricted to NK cell and CD8+ T cell biology. Knocking-

out immunoevasins represents a critical step to engineer viruses for experimental or therapeutic purposes, making them safer and more stable. On the other hand, viruses can be engineered for the expression of immunoevasins, as in type 1 diabetes. In this context, the lentiviral vector leads the expression of US2 protein of hCMV in beta pancreatic cells to avoid their autoimmune killing. Studies on HCV immune evasion revealed a mechanism by which the viral protease NS3/4A disrupts MAVS, avoiding IRF3-mediated antiviral response. We propose a novel mechanism to protect the host against the excessive inflammation occurring upon delayed type 1 IFN response in SARS pathogenesis by impairing mitochondrial antiviral signaling and subsequent IFN-I production.

Quarantine Evaders

Benedetta Mattorre, Flavia Trionfetti, Erica Parisi, Magdalini Alexandridi, Francesco Castagna

Many viruses have developed elegant strategies to evade the host immune system. Among these, viral immunoevasins are proteins acting as inhibitors of virtually all the stages of the MHC class I antigen processing and presentation pathway (preventing CD8+ CTLs-mediated killing of virus infected cells). Therefore, they in first place represent a great research tool to dissect most features and steps of adaptive immunity. Moreover, immunoevasins have potential use in studying the antigen processing of new vaccine formulations; in the generation/discovery of TEIPPs on tumor or virus-infected cells as targets for immunotherapy; and in limiting the immunogenicity of viral gene therapy vectors' proteins by inserting proteasomal degradation preventing Gly-Ala repeats (as in EBNA-1).

Viral Dodgers

Arianna Pastore, Daniela Paira, Andrea Mariancini and Agnese Rumolo

To allow a wider use of viral vectors in patients, various strategies have been defined to subdue deleterious innate and adaptive immune responses, that represent an obstacle for their clinical use. Several possible solutions may be implicated, such as blockage of specific cytokines (IL-1, IL-6, or T1 IFN) and vector engineering. One of the new applications is aimed at designing an adeno-associated viral vector (AAVV) with a selective tropism for medullary Thymic Epithelial Cells (mTEC). mTECs could induce a mechanism of tolerance versus

specific viral antigens through the presentation of tissue restricted antigens (TRAs), which determines the clonal deletion of positive T-cells.

Can't wait for May 4th

Marcella Franco, Gloria Tucci, Lorenzo Cuollo and Junbiao Wang

CMV is the paradigm of the ability of viruses to escape immune surveillance, being able to impair possibly every known pathway of innate and adaptive immune response. The complete knowledge of viral genome could be exploited to create "rationally" attenuated viruses, which lack specific genes encoding for immunoevasins, using them as a safe vaccine. Such strategy would preserve the antigenic potential of the virus, while weakening its virulence and ability to reactivate from latency. The study of SARS-CoV2 immunoevasins, which are still poorly known, could in principle allow similar vaccine strategy and might as well explain the apparent lack of immunological memory observed in some patients.

VirTool

Elena Messina, Matteo Gallazzi and Maria Anele Romeo

Virus engineering shows us an interesting scenario in pathological treatments. Oncolytic virus therapies, whose mechanism is based on infection and death of targeted cells, may be used in oncological therapy. Moreover, MHC class-I gene may be downregulated in malignant cells by engineered viruses to allow immune system response, as in the case of mono-genetic disorders treatment, since it allows both corrective delivery and the restore of defective genes. Furthermore, they could serve as vaccine delivery agents since they are able to bypass the host immune system by evading the viral receptors recognition during infection by the host to reach the goal.

The ACEmptomatics

Anne Lise Ferrara, Francesca Romana Liberati, Fabiola Vacca, Mariantonia Braile, Luisa Loconte and Bianca Cinicola

The evolution of large DNA viruses, such as Cytomegalovirus, has allowed the adaptation of MHC-I fold for immunoevasine function. Immunoevasins can act through different mechanisms of action (eg., molecular mimics, convergent immunoevasin, alternative binders). Based on recent observations, potential

benefits could be reached by studying these immunoevasion mechanisms. The excessive inflammation, autoimmunity or transplantation are characterized by excessive inflammation and the dampening of immune system could represent a therapeutic application. Therefore, in these conditions, viral immunoevasins might represent a new class of therapeutic agents and potentially a source of selective and potent immunomodulatory molecules.

Break out peas

Luca Modestino, Michele Tufano, Prisca Mauro, Beatrice Ludovica Ritondo, Valentino Ribecco

Immunoevasins are viral proteins that help virus to escape from immune surveillance. CMV is an expert at immune evasion, and by means of immunoevasins, it is able to prevent antigen presentation to CD8+ and CD4+ T-cells. Intriguingly, recombinant CMV viruses are now being explored as potential vaccine vectors to generate large numbers of T-cells against cancer. Given that tumors are immuno-suppressive microenvironments, the in-situ delivery of CMV vectors devoid of viral immune evasion genes could boost the immune system against tumor cells. Moreover, CMV encodes a group of FCyR binding glycoproteins able to inhibit the host response, by attenuating the ADCC of NK cells, which may be useful in transplants or in autoimmunity.

Evasin is the new black

Ludovica Di Martino, Sara Magri, Simone Frascolla, Alessia Ametrano, Giulia Siena, Diego Ulisse Pizzagalli

Viruses could be powerful tools in transplantation. Indeed, a central issue for transplantation is the life-long modulation of the recipient's immune response with immunosuppressive drugs. A promising strategy could be achieved by using viral vectors as gene therapy. Amongst these, Human Herpes Virus (HHV) infection persists in the host conferring long lasting immune modulation. HHV encodes some viral microRNAs with immunoevasin-like activities which play a crucial role in mediating NK cell inhibition, interfering with MHC-I antigen presentation and with TLR-signaling. Therefore, HHV gene therapy can be used for generating non-immunogenic cells in order to avoid graft rejection.

Chapter 5

Which arm of the immune system (innate vs adaptive) is more important in host defense? Why?

Prof. Matteo Iannacone

The Innate Defenders

Daniela Ricci, Francisca Venegas, Cristina Liboni, Giorgia Paldino, Benedetta Sposito, Miriam Capra and Junbiao Wang

The innate immune system represents the first independent line of defense against pathogens. Its outstanding importance is emphasized by its ancestral origin: every multicellular organism has an innate immune response while adaptive immunity emerged for the first time in vertebrates. The adaptative immune system depends on somatic diversification of antigen-receptor genes to generate a vast repertoire of cells with the advantage of plasticity and immunological memory. However, adaptive immunity relies on the innate immune system for activation through antigen presentation. Moreover, the release of soluble factors (e.g. cytokines, lectins, pentraxins and complement-related proteins) drives adaptive cell functions and promotes the growth of their response over time.

Innate defenders

Giulia Siena, Stefano Gianoli, Francesca Romana Liberati, Alice Masserdotti and Eleonora Martinis

The innate immune system is the first defense to prevent pathogens invasion and replication before more specific protection by the adaptive immune system is generated. The innate immunity is present since birth and it is a quick non-specific response not affected by environment, and it does not require repeated exposure to pathogens. Moreover, innate immune signals play a critical role in initiating and instructing the development of adaptive effector mechanisms. Thus, they are strictly intertwined and both essential in the immune response. However, given the aforementioned features and considering viral infections, the innate one seems to be more important. Especially in SARS-CoV-2, the innate branch seems to be a crucial factor to prevent the progression of the disease.

Innateologists

Benedetta Mattorre, Ersilia Vinci, Simone Marcella, Lorenzo Cuollo, Sara Andreone, Mariantonia Braile, Simone Frascolla and Julija Mazej

In the animal kingdom less than 5% of all the species (in fact, only the vertebrates) possess adaptive immunity, whereas innate immunity is ubiquitous. Adaptive immunity is therefore a "luxury" that is not strictly necessary for life to exist. The innate immune response is the first line of defense against pathogens, transformed cells and tissue damage. Moreover, the establishment of adaptive immunity is rigorously dependent on pathways triggered by invariant receptors in APCs. Mammals with SCID-like conditions, completely lacking adaptive immunity, are still vital despite the low fitness. It is not possible to create a SCID-analogue for innate immunity, but such condition would probably be incompatible with life. Hence, in our view, innate immunity is more important.

Innate passion

Agnese Rumolo, Andrea Mariancini, Riccardo Capecchi, Anna Rigatelli and Alessandra Testa

Although adaptive immune responses are certainly more potent and specialized, they may be insufficient without an early, efficient innate response. The latest provides signals (release of co-stimulators, cytokines and complement activation) which determine the activation, proliferation and differentiation of adaptive immune cells. Also, most multicellular organisms exclusively depend on innate immunity. Several studies have shown that deficiencies in innate immune mechanisms increase susceptibility to infections; in the absence of an innate immune system, the acquired immune response offers weak protection. This circumstance is particularly evident in those patients that have inadequate numbers of circulating granulocytes. Moreover, the innate response is vital for newborns; premature infants display markedly impaired innate immune functions, which likely account for their propensity to develop bacterial sepsis during the neonatal period associated with elevated mortality.

Inn8 Immunity

Laura Cogrossi, Chiara Dal Secco, Laura Grassi, Mariavittoria Laezza, Elena Messina, Maria Pozzi, Maria Anele Romeo and Flavia Trionfetti

Communication between innate and adaptive immunity is fundamental to protect against infection, however innate immunity is necessary for the immune response to start. The innate immune system is an evolutionarily conserved host defense system, conversely adaptive immunity is present only in vertebrates. The innate immunity is a first line of defense, critical to determine a prompt response against non-self pathogens, even without previous exposure. As a result, viruses developed lots of escape mechanisms to innate defense, such as the increase of proteases that cleave STING or MAVS to block IFN-I production. Moreover, the adaptive response cannot occur without an innate immune system. All this evidences makes innate immune response very important, although this does not make the adaptive less relevant.

PAC-MAN

Anna Pasotti, Matteo Gallazzi, Linda Barbieri, Daniela Paira, Federica Farina and Evangelia Beslika

It is better to fight the front-line enemy than to let him enter home. The innate immune system is the first line of defense against infection (non-self) or tissue injury (damaged self). Speed is a defining characteristic of innate immunity: within minutes of pathogen exposure, it starts generating a protective inflammatory response. Due to non-specialization, each cell reacts to a variety of 'threats' during lifetime but at the same time it is self-tolerant. Moreover, it can be triggered without the selective events that underlie adaptive immunity, which is characterized by antigen-specificity and immunological memory. As a proof of the impressive protective capacity of this immunity, we have to consider that only vertebrates boast the added benefits of an adaptive immunity, leaving most organisms on our planet to survive on innate immunity alone.

Immunità 1 - Immunità 2

Giuseppe Pietropaolo, Dario Cardamone, Roberta Manco, Luca Modestino,Prisca Mauro and Chiara Cioccarelli

Innate and adaptive immunity act as two pages of the same book, integrating completely and working together. The innate immune system represents the first line of response against pathogens. The importance of innate immune system is demonstrated by the role of innate immune cells for lymphoid organs formation and for an appropriate adaptive immune response. Moreover, since the discovery of ILC that produce cytokines typically attributed to T helper cells, the role of the innate immune system has been emphasized. Adaptive immunity, while slower to develop compared with innate immunity, is pathogen-specific and allows a more rapid and effective response in the case of reinfections although also for NK cells it was reported the ability to generate memory cells.

Silly Italian Immunologists Creating Acronyms

Amanda Facoetti, Sara Bozzer, Luca Mezzanzanica, Diego Ulisse Pizzagalli and Francesco Castagna

Finely tuned cooperation between all the players of the immune system makes the difference between life and death. While innate immunity provides first non-specific line of defense upon the challenge of a pathogen, later on it is the job of the adaptive immunity to effectively eradicate the threat with a pathogen-tailored strategy and to build up a long-lasting memory to promptly react and thus prevent reinfections. The paramount importance of each arm of immunity is proved by the fact that congenital or acquired immunodeficiencies affecting even only one component of the immune system are major predisposing causes of infection, reduced life expectancy and death. Moreover, given the adaptive-like function played by some innate cells (antigen-specific NK memory cells) and the physiological continuous cross-talk between the two arms, the dichotomic paradigm of immunology is being revised.

HostBusters

Magda Alexandridi, Bianca Cinicola, Sharon Eleuteri, Marcella Franco and Fabiola Vacca

Both innate and adaptive immune systems are fundamental to obtain a rapid and specific response respectively, therefore we should not consider them as two different and separate arms since they empower each other. During an infection innate immunity is the first to be triggered and then, cytokines secretion and APCs activate adaptive immunity's lymphocytes. These cells, in turn, enhance innate immune cells capacity. e.g. phagocytes recognize and incorporate better opsonized microbes. Moreover, adaptive immunity is essential in secondary infections or in vaccination, however most vaccine adjuvants increase the antigen-specific immune response by acting on PRRs receptors of innate immunity. Pathogens developed various escape mechanisms over time (pneumococcal capsular polysaccharide inhibits phagocytosis, herpesvirus inhibits MHC I and pro-inflammatory cytokine synthesis) but the host-immune system evolved too, both with the well-known adaptive immunity and also through the lately discovered "trained immunity" in an epigenetic-dependent manner. Hence, innate and adaptive immunity cooperate and co-evolve over time in order to face the escape mechanisms continuously developed by pathogens.

The Game of Immunity

Valentino Ribecco, Valentina Orticelli, Chiara Di Censo, Laura Musa, Gloria Tucci and Andrea Uva

Innate immunity is a powerful system to counteract pathogen invasion, but also transformed and mechanically damaged cells, in order to maintain homeostasis. The importance of innate immunity is due to the fact that the recognition of foreign antigens is not necessary for its activation. Moreover, a proper adaptive response would not be able to be mounted without innate immunity. Furthermore, its triggering is very fast and efficient and most of the infections can be eradicated just with its intervention. Finally, it is responsible of producing a variety of cytokines and chemokines that creates an inflammatory environment essential to resolve the damage.

Quentin Quarantine-o

Beatrice Ludovica Ritondo, Erica Parisi, Elisabetta Marcuzzi, Anne Lise Ferrara, Arianna Pastore, Anna Vanni and Ludovica Timperi

Host innate immunity represents the first strategy of defense against infectious pathogens and is immediate, non-specific and evolutionarily conserved. Natural immunity triggers a wide spectrum of molecular pathways including the production of cytokines and chemokines, the activation of complement cascade, and the induction of the adaptive immune response, which is a late, complex and specific response, characterized by immunological memory. However, the ability to respond more robustly against a second encounter with the same pathogen has been described also in several innate immune cells such as NK cells and ILCs. This “trained immunity,” could be a primitive form of adaptation of host defense through epigenetic modifications. These and other aspects of innate immunity make it an essential arm the immune system.

Cytoking

Francesco Gasperoni

To cut a long story short, without the innate immune system we cannot exist, without the adaptive we cannot survive. The innate immune system is a very general 'first line' of defense, a nonspecific defense mechanisms against the external environment that come into play within hours of an antigen's appearance in the body or immediately if we mention the Anatomo-Physiological features as skin, mucous membranes, temperature , pH, chemicals, etc. Without such features we could not exist as an organism because we could not even maintain our internal homeostasis, and therefore there would be no difference between the internal and external environment. The adaptive immune response processes the antigen and recognizes it and then, once the antigen has been recognized, it creates an army of immune cells specifically designed to attack that antigen also memorizing the process. Without an adaptive immune system an organism would have to live in a sterile isolated environment for all of his life. But he would be alive.

Chapter 6

What can be done in vaccine research to be more prepared for the next pandemic?

Prof. Ennio De Gregorio

Peter Pan-demic

Daniela Paira, Linda Barbieri, Gianluca Scarno, Beatrice Ludovica Ritondo, Laura Grassi, Giuseppe Pietropaolo and Nicolò Morina

Since it is almost impossible to predict which virus might cause the next pandemic, it is essential to design panviral vaccines, effective against a wide range of strains. Historically, viral pandemics arise from the spread of a new serotype of a known virus which becomes infective for humans. Therefore, a wide knowledge of viral structure and its conservation among serotypes is critical and allows the identification of domains to be used as shared epitopes. Recently, a number of prospective universal flu vaccines have been developed that work by targeting the stalk domain and not its globular head, which mutates easily. Beside biological knowledge, production capacity and vaccine distribution should be optimized. New molecules may be the solution; a cutting-edge approach is represented by mRNA vaccines, which can be rapidly produced on a vast scale and are extremely adaptable to the pathogen.

Shot me down

Francesca Biscu, Federica Farina, Cristina Liboni, Martina Morandi, Laura Cogrossi, Francesco Castagna

Preparedness is key to a rapid and effective response to a new pandemic infectious disease. In order to achieve this goal, several actions should be taken, such as: implementing old and establishing new platforms for designing more immunogenic antigen formulations (adjuvant-containing, conjugated, VLPs-linked) possibly to be used in combination for a better response; developing novel approaches for the delivery (liposomes, infectious material, polymeric particles) and administration of the vaccine (electroporation, sonophoresis, iontophoresis). In the early phase, it would be also auspicable to rely on standardized *in vitro* and *in vivo* systems, representative of the pathogenesis and

the viral tropism involved. Later on, improvement and scale-up of the bioprocessing steps are highly needed to fulfill the global demand in the shortest time.

Panviral

Francisca Venegas, Magda Alexandridi, Elena Messina and Annica Barizza

Considered that it is almost impossible to predict which virus might cause the next pandemic, probably the best thing to do is to design panviral vaccines that would be effective against a wide range of strains: all types of influenza, for instance, or a substantial group of coronaviruses rather than just one. In recent years, panviral vaccines are becoming a real possibility, a number of prospective universal flu vaccines have been developed, they work by targeting virus's parts which barely mutate at all. Another approach could be to deepen the studies on mRNA vaccines. Their advantages are potentially enormous, in part because they can be made in less time than other vaccines but also because they can be made on a vast scale. They are extremely adaptable too, in fact, they are easy to redesign for the next virus.

Let's be prepared for the next pandemic: research is the solution

Ersilia Vinci, Giulia Siena, Miriam Capra and Eleonora Martinis

To be more prepared for the next pandemic, firstly we should accelerate the selection process of common antigens for vaccines that deliver immunity to the multiple strains of the same virus/bacterium that are already present. To achieve this, we should identify genetically stable epitopes which then may be conserved also in the future. To do that, taking advantage of reverse vaccinology, we should isolate antibodies from previously infected individuals with different strains, characterize such Abs for the identification of epitopes conserved among strains and design vaccines based on such epitopes which could work also for mutated forms that will appear. Secondly, we should evaluate possible complications like immune enhancement (i.e. ADE) from previous experiences and finally, a global homogeneity of vaccines distribution and availability is another important point to consider.

SPILLtheteaOVER

Ludovica Timperi, Prisca Mauro, Marcella Franco, Maria Anele Romeo, Anna Vanni, Alessandra Testa, Chiara Dal Secco and Julija Mazej

The anticipation of new pandemic, caused by zoonotic viruses capable of a spillover, may accelerate the process of vaccine development: genome sequencing, next-generation approaches and protein analysis of possible targets could be done even before the outbreak takes place to give us a time advantage. The novel platforms based on DNA or mRNA offer great flexibility in terms of antigen manipulation and potential for speed. It is also crucial to exploit the considerable potential of the new technologies to produce immunity against pathogens for which traditional vaccination has failed. An example is the use of CRISPR-Cas9 to genetically reprogram B cells to produce, and keep producing, whatever antibody someone needs.

Prevention is mej che cure

Daniela Ricci, Benedetta Sposito, Mariavittoria Laezza, Erica Parisi, Luana Tomaipitinca and Junbiao Wang

Development of vaccines against pathogens is pivotal to contain and prevent pandemics. One approach is to try to predict a priority list of pathogens which are most likely to cause global outbreaks, although several epidemics such as HIV or Zika could not be anticipated. Therefore, it can be useful to also identify specific and optimal platforms for each different microorganism family and promising common molecules to be targeted. Additionally, investments should be made to develop platforms that can be rapidly adapted to different pathogens as well as adjuvants to enhance the immune response, avoid multiple boosts and reduce antigen dose. Finally, executing clinical trial phases and manufacturing in parallel can accelerate vaccine availability.

May the 4th be with you

Chiara Di Censo, Valentino Ribecco, Sara Coletta, Anna Rigatelli, Chiara Cioccarelli, Diego Ulisse Pizzagalli and Matteo Gallazzi

We do not know when or where, but we expect future deadly viral infection will strike. Therefore, designing pan-viral vaccines and surveilling the most likely sources of zoonotic disease are successful strategies. Initiatives like CEPI have

started to focus on this topic. Moreover, novel technologies are available and can be applied to reduce vaccine development time. Among these, Artificial Intelligence can predict the next viral outbreak as well as identify groups of patients that require specific vaccination strategies. Additionally, viral vectors and Self-Amplifying mRNA, may allow to enhance vaccine effectiveness. Lastly, we should ask ourselves how to ensure that media and individual national governments can fully assimilate the importance of vaccine research.

The Next Big One

Sara Virtuoso, Anne Lise Ferrara, Gloria Tucci, Maria Pozzi, Arianna Pastore and Amanda Facoetti

The Next Big One" is a recurring theme for scholars nowadays, if they want to stop the next pandemic they're best bet is catching emerging viruses at the source: in a wildlife reservoir. Unfortunately, it is not possible to find them all and study their viral strategies. Many novel vaccination strategies should be improved to rapidly ramp up production of an effective vaccine, focusing on safe administration and long-lasting efficacy immune responses. Gene-based antigen-delivery technologies, has shown promise in protective humoral and cellular immunity in animal model; but DNA technology still not been approved for human use due to his theoretically uncontrolled stimulation of the host genes. To overcome this restrictions, recently use of mRNA-based vaccine, that does not exert the possibility of genome integration, offers considerable potential. Moreover, Liposome-mediated vaccine delivery, a non-viral vector, provides greater efficacy and safer vaccine formulation for human use. Much has already been done, but much still needs to be done.

Vax Wars

Alessia Ametrano, Flavia Trionfetti, Giorgia Paldino, Lorenzo Cuollo and Sara Bozzer

The situation we are now living shows us how much cooperation and standardization in scientific research are fundamental. In this light, expanding databases of conserved pathogen sequences could speed up vaccine development, allowing the sharing of information between countries, including genomic sequences, 3D protein structures and isolation protocols. This contributes to create a general platform that can be adapted to every antigen, such as viral vectors or self-amplifying RNA delivery systems. Moreover, the

genetic sequences stored in the database could be used as platforms to develop more rapid DNA or RNA vaccines, as it has been done for the FDA-licensed Ebola vaccine, where another virus was used as a platform with the requisite Ebola protein inserted.

Tommaso's

Riccardo Capecchi, Simone Frascolla, Francesca Romana Liberati, Elisabetta Marcuzzi, Luca Modestino, Laura Musa, Evangelia Beslika and Andrea Uva

Due to the need for prediction of possible future pandemics, it is necessary to improve epidemiological research. Viruses use receptors to enter human cells, which are optimal targets for vaccination (e.g. spike protein). Selection of hypothetical peptides, interacting with human cell-surface proteins and development of monoclonal antibodies against them, can lead to identification of immunodominant antigenic sites associated with neutralization. This can provide reagents for stabilizing and solving the structure of viral surface proteins, guiding to the selection of vaccine targets. Safety, effectiveness, fast development (technologies as RNA vaccines or baculovirus vector), testing (e.g. controversial proposal about testing in group of healthy volunteers, by taking a pilot vaccine and subsequently get infected) and massive production time, are pivotal characteristics for the next pandemic vaccine.

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