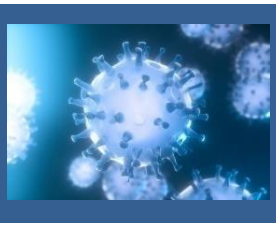
COVID-19

Aug 12 – 18, 2021



RESEARCH PUBLICATIONS

Publication Date: Aug 18, 2021

Protective antibodies elicited by SARS-CoV-2 spike protein vaccination are boosted in the lung after challenge in nonhuman primates

Adjuvanted soluble protein vaccines have been used extensively in humans for protection against various viral infections based on their robust induction of antibody responses. Here, soluble prefusion-stabilized spike protein trimers (preS dTM) from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were formulated with the adjuvant AS03 and administered twice to nonhuman primates (NHPs). Binding and functional neutralization assays and systems serology revealed that the vaccinated NHP developed AS03-dependent multifunctional humoral responses that targeted distinct domains of the spike protein and bound to a variety of Fc receptors mediating immune cell effector functions *in vitro*. The neutralizing 50% inhibitory concentration titers for pseudovirus and live SARS-CoV-2 were higher than titers for a panel of human convalescent serum samples. NHPs were challenged intranasally and intratracheally with a high dose (3 × 106 plaque forming units) of SARS-CoV-2 (USA-WA1/2020 isolate). Two days after challenge, vaccinated NHPs showed rapid control of viral replication in both the upper and lower airways. Vaccinated NHPs also had increased spike protein–specific immunoglobulin G (IgG) antibody responses in the lung as early as 2 days after challenge. Moreover, passive transfer of vaccine-induced IgG to hamsters mediated protection from subsequent SARS-CoV-2 challenge. These data show that antibodies induced by the AS03-adjuvanted preS dTM vaccine were sufficient to mediate protection against SARS-CoV-2 in NHPs and that rapid anamnestic antibody responses in the lung may be a key mechanism for protection.

Reference

https://www.science.org/doi/10.1126/scitranslmed.abi4547

Yeast-produced RBD-based recombinant protein vaccines elicit broadly neutralizing antibodies and durable protective immunity against SARS-CoV-2 infection

Abstract

Massive production of efficacious SARS-CoV-2 vaccines is essential for controlling the ongoing COVID-19 pandemic. It was reported here that the preclinical development of yeast-produced receptor-binding domain (RBD)-based recombinant protein SARS-CoV-2 vaccines. It was found that monomeric RBD of SARS-CoV-2 could be efficiently produced as a secreted protein from transformed *Pichia pastoris* (*P. pastoris*) yeast. Yeast-derived RBD-monomer possessed functional conformation and was able to elicit protective level of neutralizing antibodies in mice. It was further designed and expressed a genetically linked dimeric RBD protein in yeast. The engineered dimeric RBD was more potent than the monomeric RBD in inducing long-lasting neutralizing antibodies. Mice immunized with either monomeric RBD or dimeric RBD were effectively protected from live SARS-CoV-2 virus challenge even at 18 weeks after the last vaccine dose. Importantly, it was found that the antisera raised against the RBD of a single SARS-CoV-2 prototype strain could effectively neutralize the two predominant circulating variants B.1.1.7 and B.1.351, implying broad-spectrum protective potential of the RBD-based vaccines. The data demonstrate that yeast-derived RBD-based recombinant SARS-CoV-2 vaccines are feasible and efficacious, opening up a new avenue for rapid and cost-effective production of SARS-CoV-2 vaccines to achieve global immunization.

Reference

https://www.nature.com/articles/s41421-021-00315-9

The size and culturability of patient-generated SARS-CoV-2 aerosol

Abstract

Background: Aerosol transmission of COVID-19 is the subject of ongoing policy debate. Characterizing aerosol produced by people with COVID-19 is critical to understanding the role of aerosols in transmission.

Objective: The presence of virus was investigated in size-fractioned aerosols from six COVID-19 patients admitted into mixed acuity wards in April of 2020.

Methods: Size-fractionated aerosol samples and aerosol size distributions were collected from COVID-19 positive patients. Aerosol samples were analyzed for viral RNA, positive samples were cultured in Vero E6 cells. Serial RT-PCR of cells indicated samples where viral replication was likely occurring. Viral presence was also investigated by western blot and transmission electron microscopy (TEM).

Results: SARS-CoV-2 RNA was detected by rRT-PCR in all samples. Three samples confidently indicated the presence of viral replication, all of which were from collected sub-micron aerosol. Western blot indicated the presence of viral proteins in all but one of these samples, and intact virions were observed by TEM in one sample.

Significance: Observations of viral replication in the culture of submicron aerosol samples provides additional evidence that airborne transmission of COVID-19 is possible. These results support the use of efficient respiratory protection in both healthcare and by the public to limit transmission.

Reference

https://www.nature.com/articles/s41370-021-00376-8

Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children

Abstract

Children have reduced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rates and a substantially lower risk for developing severe coronavirus disease 2019 compared with adults. However, the molecular mechanisms underlying protection in younger age groups remain unknown. Here the single-cell transcriptional landscape

was characterized in the upper airways of SARS-CoV-2-negative ($n = 18$) and age-matched SARS-CoV-2-positive ($n = 24$) children and corresponding samples from adults ($n = 44$), covering an age range of 4 weeks to 77 years. Children displayed higher basal expression of relevant pattern recognition receptors such as MDA5 (*IFIH1*) and RIG-I (*DDX58*) in upper airway epithelial cells, macrophages and dendritic cells, resulting in stronger innate antiviral responses upon SARS-CoV-2 infection than in adults. We further detected distinct immune cell subpopulations including *KLRC1* $(NKG2A)^+$ cytotoxic T cells and a $CD8^+$ T cell population with a memory phenotype occurring predominantly in children. The study provides evidence that the airway immune cells of children are primed for virus sensing, resulting in a stronger early innate antiviral response to SARS-CoV-2 infection than in adults.

Reference

https://www.nature.com/articles/s41587-021-01037-9

HIF-1α promotes SARS-CoV-2 infection and aggravates inflammatory responses to COVID-19

Abstract

The Cytokine storm induced by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a major pathological feature of Coronavirus Disease 2019 (COVID-19) and a crucial determinant in COVID-19 prognosis. Understanding the mechanism underlying the SARS-CoV-2-induced cytokine storm is critical for COVID-19 control. Here, it was identified that SARS-CoV-2 ORF3a and host hypoxia-inducible factor-1α (HIF-1α) play key roles in the virus infection and pro-inflammatory responses. RNA sequencing shows that HIF-1α signaling, immune response, and metabolism pathways are dysregulated in COVID-19 patients. Clinical analyses indicate that HIF-1α production, inflammatory responses, and high mortalities occurr in elderly patients. HIF-1α and pro-inflammatory cytokines are elicited in patients and infected cells. Interestingly, SARS-CoV-2 ORF3a induces mitochondrial damage and Mito-ROS production to promote HIF-1α expression, which subsequently facilitates SARS-CoV-2 infection and cytokines production. Notably, HIF-1α also broadly promotes the infection of other viruses. Collectively, during SARS-CoV-2 infection, ORF3a induces HIF-1α, which in turn aggravates viral infection and inflammatory responses. Therefore, HIF-1α

plays an important role in promoting SARS-CoV-2 infection and inducing pro-inflammatory responses to COVID-19.

Reference

https://www.nature.com/articles/s41392-021-00726-w

A simple and fast spectroscopy-based technique for COVID-19 diagnosis

Abstract

The coronavirus pandemic, which appeared in Wuhan, China, in December 2019, rapidly spread all over the world in only a few weeks. Faster testing techniques requiring less resources are key in managing the pandemic, either to enable larger scale testing or even just provide developing countries with limited resources, particularly in Africa, means to perform tests to manage the crisis. Here, an unprecedented, rapid, reagent-free and easy-to-use screening spectroscopic method was reported for the detection of SARS-CoV-2 on RNA extracts. This method, validated on clinical samples collected from 280 patients with quantitative predictive scores on both positive and negative samples, is based on a multivariate analysis of FTIR spectra of RNA extracts. This technique, in agreement with RT-PCR, achieves 97.8% accuracy, 97% sensitivity and 98.3% specificity while reducing the testing time post RNA extraction from hours to minutes. Furthermore, this technique can be used in several laboratories with limited resources.

Reference

https://www.nature.com/articles/s41598-021-95568-5

Longitudinal analysis of antibody decay in convalescent COVID-19 patients

Abstract

Determining the sustainability of antibodies targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is essential for predicting immune response against the Coronavirus disease 2019 (COVID-19). To quantify the antibody decay rates among the varying levels of anti-nucleocapsid (anti-N) Immunoglobulin G (IgG) in convalescent COVID-19 patients and estimate the length of time they maintained SARS-CoV-2

specific antibodies, longitudinal blood samples were collected from 943 patients over the course of seven months after their initial detection of SARS-CoV-2 virus by RT-PCR. Anti-N IgG levels were then quantified in these blood samples. The primary study outcome was the comparison of antibody decay rates from convalescent patients with high or low initial levels of antibodies using a mixed linear model. Additional measures include the length of time that patients maintain sustainable levels of anti-N IgG. Antibody quantification of blood samples donated by the same subject multiple times shows a gradual decrease of IgG levels to the cutoff index level of 1.4 signal/cut-off (S/C) on the Abbott Architect SARS-CoV-2 IgG test. In addition, this study shows that antibody reduction rate is dependent on initial IgG levels, and patients with initial IgG levels above 3 S/C show a significant 1.68-fold faster reduction rate compared to those with initial IgG levels below 3 S/C. For a majority of the donors naturally occurring anti-N antibodies were detected above the threshold for only four months after infection with SARS-CoV-2. This study is clinically important for the prediction of immune response capacity in COVID-19 patients.

Reference

https://www.nature.com/articles/s41598-021-96171-4

A potently neutralizing SARS-CoV-2 antibody inhibits variants of concern by utilizing unique binding residues in a highly conserved epitope

Abstract

With the emergence of SARS-CoV-2 variants with increased transmissibility and potential resistance, antibodies and vaccines with broadly inhibitory activity are needed. Here a panel of neutralizing anti-SARS-CoV-2 monoclonal antibodies (mAbs), was developed that bound the receptor binding domain of the spike protein at distinct epitopes and blocked virus attachment to its host receptor, human angiotensin converting enzyme-2 (hACE2). Although several potently neutralizing mAbs protected K18-hACE2 transgenic mice against infection caused by ancestral SARS-CoV-2 strains, others induced escape variants in vivo or lost neutralizing activity against emerging strains. One mAb, SARS2-38, potently neutralized all SARS-CoV-2 variants of concern tested and protected mice against challenge by multiple SARS-CoV-2 strains. Structural analysis showed that SARS2-38 engaged a conserved epitope proximal to the receptor

binding motif. Thus, treatment with or induction of neutralizing antibodies that bind conserved spike epitopes may limit the loss of potency of therapies or vaccines against emerging SARS-CoV-2 variants.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00348-4

The origins of SARS-CoV-2: A critical review

Abstract

Since the first reports of a novel severe acute respiratory syndrome (SARS)-like coronavirus in December 2019 in Wuhan, China, there has been intense interest in understanding how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in the human population. Recent debate has coalesced around two competing ideas: A “laboratory escape” scenario and zoonotic emergence. Here, the current scientific evidence was critically reviewed that may help clarify the origin of SARS-CoV-2.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00991-0

The interferon landscape along the respiratory tract impacts the severity of COVID-19

Abstract

Severe COVID-19 is characterized by overproduction of immune mediators, but the role of interferons (IFNs) of the type I (IFN-I) or type III (IFN-III) families remains debated. The production of IFNs was scrutinized along the respiratory tract of COVID-19 patients and found that high levels of IFN-III, and to a lesser extent IFN-I, characterize the upper airways of patients with high viral burden but reduced disease risk or severity. Production of specific IFN-III, but not IFN-I, members, denotes patients with a mild pathology and efficiently drives the transcription of genes that protect against SARS-CoV-2. In contrast, compared to subjects with other infectious or non-infectious lung pathologies, IFNs are over-represented in the lower airways of patients with severe COVID-19 that exhibit gene pathways associated with increased apoptosis and

decreased proliferation. The data demonstrated a dynamic production of IFNs in SARS-CoV-2-infected patients and show IFNs play opposing roles at distinct anatomical sites.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00990-9

Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces viral shedding after SARS-CoV-2 D614G challenge in preclinical models

Abstract

ChAdOx1 nCoV-19/AZD1222 is an approved adenovirus-based vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) currently being deployed globally. Previous studies in rhesus macaques revealed that intramuscular vaccination with ChAdOx1 nCoV-19/AZD1222 provided protection against pneumonia but did not reduce shedding of SARS-CoV-2 from the upper respiratory tract. Here, it was investigated whether intranasally administered ChAdOx1 nCoV-19 reduces detection of virus in nasal swabs after challenging vaccinated macaques and hamsters with SARS-CoV-2 carrying a D614G mutation in the spike protein. Viral loads in swabs obtained from intranasally vaccinated hamsters were decreased compared to control hamsters, and no viral RNA or infectious virus was found in lung tissue after a direct challenge or after direct contact with infected hamsters. Intranasal vaccination of rhesus macaques resulted in reduced virus concentrations in nasal swabs and a reduction in viral loads in bronchoalveolar lavage and lower respiratory tract tissue. Intranasal vaccination with ChAdOx1 nCoV-19/AZD1222 reduced virus concentrations in nasal swabs in two different SARS-CoV-2 animal models, warranting further investigation as a potential vaccination route for COVID-19 vaccines.

Reference

https://www.science.org/doi/10.1126/scitranslmed.abh0755

Immune checkpoint inhibitors increase T cell immunity during SARS-CoV-2 infection

The COVID-19 pandemic has spread worldwide, yet the role of antiviral T cell immunity during infection and the contribution of immune checkpoints remain unclear. By prospectively following a cohort of 292 patients with melanoma, half of which treated

with immune checkpoint inhibitors (ICIs), we identified 15 patients with acute or convalescent COVID-19 and investigated their transcriptomic, proteomic, and cellular profiles. It was found that ICI treatment was not associated with severe COVID-19 and did not alter the induction of inflammatory and type I interferon responses. In-depth phenotyping demonstrated expansion of CD8 effector memory T cells, enhanced T cell activation, and impaired plasmablast induction in ICI-treated COVID-19 patients. The evaluation of specific adaptive immunity in convalescent patients showed higher spike (S), nucleoprotein (N), and membrane (M) antigen-specific T cell responses and similar induction of spike-specific antibody responses. The findings provide evidence that ICI during COVID-19 enhanced T cell immunity without exacerbating inflammation.

Reference

https://www.science.org/doi/10.1126/sciadv.abg4081

Age-dependent regulation of SARS-CoV-2 cell entry genes and cell death programs correlates with COVID-19 severity

Abstract

Novel coronavirus disease 2019 (COVID-19) severity is highly variable, with pediatric patients typically experiencing less severe infection than adults and especially the elderly. The basis for this difference is unclear. It was found that mRNA and protein expression of angiotensin-converting enzyme 2 (ACE2), the cell entry receptor for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19, increases with advancing age in distal lung epithelial cells. However, in humans, ACE2 expression exhibits high levels of intra- and interindividual heterogeneity. Further, cells infected with SARS-CoV-2 experience endoplasmic reticulum stress, triggering an unfolded protein response and caspase-mediated apoptosis, a natural host defense system that halts virion production. Apoptosis of infected cells can be selectively induced by treatment with apoptosis-modulating BH3 mimetic drugs. Notably, epithelial cells within young lungs and airways are more primed to undergo apoptosis than those in adults, which may naturally hinder virion production and support milder COVID-19 severity.

Reference

https://www.science.org/doi/10.1126/sciadv.abf8609

Publication Date: Aug 17, 2021

A broadly neutralizing humanized ACE2-targeting antibody against SARS-CoV-2 variants

Abstract

The successive emergences and accelerating spread of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineages and evolved resistance to some ongoing clinical therapeutics increase the risks associated with the coronavirus disease 2019 (COVID-19) pandemic. An urgent intervention for broadly effective therapies to limit the morbidity and mortality of COVID-19 and future transmission events from SARS-related coronaviruses (SARSr-CoVs) is needed. Here, an angiotensin-converting enzyme-2 (ACE2)-blocking monoclonal antibody (MAb), named h11B11, was isolated and humanized which exhibits potent inhibitory activity against SARS-CoV and circulating global SARS-CoV-2 lineages. When administered therapeutically or prophylactically in the hACE2 mouse model, h11B11 alleviates and prevents SARS-CoV-2 replication and virus-induced pathological syndromes. No significant changes in blood pressure and hematology chemistry toxicology were observed after injections of multiple high dosages of h11B11 in cynomolgus monkeys. Analysis of the structures of the h11B11/ACE2 and receptor-binding domain (RBD)/ACE2 complexes shows hindrance and epitope competition of the MAb and RBD for the receptor. Together, these results suggest h11B11 as a potential therapeutic countermeasure against SARS-CoV, SARS-CoV-2, and escape variants.

Reference

https://www.nature.com/articles/s41467-021-25331-x

Inhibiting SARS-CoV-2 infection *in vitro* by suppressing its receptor, angiotensin-converting enzyme 2, *via* aryl-hydrocarbon receptor signal

Abstract

Since understanding molecular mechanisms of SARS-CoV-2 infection is extremely important for developing effective therapies against COVID-19, it was focused on the internalization mechanism of SARS-CoV-2 *via* ACE2. Although cigarette smoke is generally believed to be harmful to the pathogenesis of COVID-19, cigarette smoke extract (CSE) treatments were surprisingly found to suppress the expression of ACE2 in HepG2 cells. It was thus tried to clarify the mechanism of CSE effects on expression of ACE2 in mammalian cells. Because RNA-seq analysis suggested that suppressive effects on ACE2 might be inversely correlated with induction of the genes regulated by aryl hydrocarbon receptor (AHR), the AHR agonists 6-formylindolo(3,2-b)carbazole (FICZ) and omeprazole (OMP) were tested to assess whether those treatments affected ACE2 expression. Both FICZ and OMP clearly suppressed ACE2 expression in a dose-dependent manner along with inducing CYP1A1. Knock-down experiments indicated a reduction of ACE2 by FICZ treatment in an AHR-dependent manner. Finally, treatments of AHR agonists inhibited SARS-CoV-2 infection into Vero E6 cells as determined with immunoblotting analyses detecting SARS-CoV-2 specific nucleocapsid protein. We here demonstrate that treatment with AHR agonists, including FICZ, and OMP, decreases expression of ACE2 via AHR activation, resulting in suppression of SARS-CoV-2 infection in mammalian cells.

Reference

https://www.nature.com/articles/s41598-021-96109-w

Protective humoral and cellular immune responses to SARS-CoV-2 persist up to 1 year after recovery

Abstract

SARS-CoV-2 vaccination has been launched worldwide to build effective population-level immunity to curb the spread of this virus. The effectiveness and duration of protective immunity is a critical factor for public health. Here, the kinetics of the SARS-CoV-2 specific immune response were reported in 204 individuals up to 1-year after recovery from COVID-19. RBD-IgG and full-length spike-IgG concentrations and serum

neutralizing capacity decreases during the first 6-months, but is maintained stably up to 1-year after hospital discharge. Even individuals who had generated high IgG levels during early convalescent stages had IgG levels that had decreased to a similar level one year later. Notably, the RBD-IgG level positively correlates with serum neutralizing capacity, suggesting the representative role of RBD-IgG in predicting serum protection. Moreover, viral-specific cellular immune protection, including spike and nucleoprotein specific, persisted between 6 months and 12 months. Altogether, our study supports the persistence of viral-specific protective immunity over 1 year.

Reference

https://www.nature.com/articles/s41467-021-25312-0

Two doses of SARS-CoV-2 vaccination induce robust immune responses to emerging SARS-CoV-2 variants of concern

Abstract

The extent to which immune responses to natural infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and immunization with vaccines protect against variants of concern (VOC) is of increasing importance. Accordingly, here antibodies and T cells of a recently vaccinated, UK cohort, alongside those recovering from natural infection were analyzed in early 2020. It was shown that neutralization of the VOC compared to a reference isolate of the original circulating lineage, B, is reduced: more profoundly against B.1.351 than for B.1.1.7, and in responses to infection or a single dose of vaccine than to a second dose of vaccine. Importantly, high magnitude T cell responses are generated after two vaccine doses, with the majority of the T cell response directed against epitopes that are conserved between the prototype isolate B and the VOC. Vaccination is required to generate high potency immune responses to protect against these and other emergent variants.

Reference

https://www.nature.com/articles/s41467-021-25167-5

Systematic profiling of SARS-CoV-2-specific IgG responses elicited by an inactivated virus vaccine identifies peptides and proteins for predicting vaccination efficacy

Abstract

One of the best ways to control COVID-19 is vaccination. Among the various SARS-CoV-2 vaccines, inactivated virus vaccines have been widely applied in China and many other countries. To understand the underlying protective mechanism of these vaccines, it is necessary to systematically analyze the humoral responses that are triggered. By utilizing a SARS-CoV-2 microarray with 21 proteins and 197 peptides that fully cover the spike protein, antibody response profiles of 59 serum samples collected from 32 volunteers immunized with the inactivated virus vaccine BBIBP-CorV were generated. For this set of samples, the microarray results correlated with the neutralization titers of the authentic virus, and two peptides (S1-5 and S2-22) were identified as potential biomarkers for assessing the effectiveness of vaccination. Moreover, by comparing immunized volunteers to convalescent and hospitalized COVID-19 patients, the N protein, NSP7, and S2-78 were identified as potential biomarkers for differentiating COVID-19 patients from individuals vaccinated with the inactivated SARS-CoV-2 vaccine. The comprehensive profile of humoral responses against the inactivated SARS-CoV-2 vaccine will facilitate a deeper understanding of the vaccine and provide potential biomarkers for inactivated virus vaccine-related applications.

Reference

https://www.nature.com/articles/s41421-021-00309-7

Repurposing the estrogen receptor modulator raloxifene to treat SARS-CoV-2 infection

Abstract

The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) necessitates strategies to identify prophylactic and therapeutic drug candidates to enter rapid clinical development. This is particularly true, given the uncertainty about the endurance of the

immune memory induced by both previous infections or vaccines, and given the fact that the eradication of SARS-CoV-2 might be challenging to reach, given the attack rate of the virus, which would require unusually high protection by a vaccine. Here, it was shown how raloxifene, a selective estrogen receptor modulator with anti-inflammatory and antiviral properties, emerges as an attractive candidate entering clinical trials to test its efficacy in early-stage treatment COVID-19 patients.

Reference

https://www.nature.com/articles/s41418-021-00844-6

Dynamic landscape mapping of humoral immunity to SARS-CoV-2 identifies non-structural protein antibodies associated with the survival of critical COVID-19 patients

Abstract

A comprehensive analysis of the humoral immune response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is essential in understanding COVID-19 pathogenesis and developing antibody-based diagnostics and therapy. In this work, a longitudinal analysis of antibody responses was performed to SARS-CoV-2 proteins in 104 serum samples from 49 critical COVID-19 patients using a peptide-based SARS-CoV-2 proteome microarray. The data show that the binding epitopes of IgM and IgG antibodies differ across SARS-CoV-2 proteins and even within the same protein. Moreover, most IgM and IgG epitopes are located within nonstructural proteins (nsps), which are critical in inactivating the host's innate immune response and enabling SARS-CoV-2 replication, transcription, and polyprotein processing. IgM antibodies are associated with a good prognosis and target nsp3 and nsp5 proteases, whereas IgG antibodies are associated with high mortality and target structural proteins (Nucleocapsid, Spike, ORF3a). The epitopes targeted by antibodies in patients with a high mortality rate were further validated using an independent serum cohort ($n = 56$) and using global correlation mapping analysis with the clinical variables that are associated with COVID-19 severity. The data provide fundamental insight into humoral immunity during SARS-CoV-2 infection. SARS-CoV-2 immunogenic epitopes identified in this work could also help direct antibody-based COVID-19 treatment and triage patients.

Reference

https://www.nature.com/articles/s41392-021-00718-w

Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in people living with and without HIV in South Africa: An interim analysis of a randomised, double-blind, placebo-controlled, phase 1B/2A trial

Abstract

Background: People living with HIV are at an increased risk of fatal outcome when admitted to hospital for severe COVID-19 compared with HIV-negative individuals. It was aimed to assess safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in people with HIV and HIV-negative individuals in South Africa.

Methods: In this ongoing, double-blind, placebo-controlled, phase 1B/2A trial (COV005), people with HIV and HIV-negative participants aged 18–65 years were enrolled at seven South African locations and were randomly allocated (1:1) with full allocation concealment to receive a prime-boost regimen of ChAdOx1 nCoV-19, with two doses given 28 days apart. Eligibility criteria for people with HIV included being on antiretroviral therapy for at least 3 months, with a plasma HIV viral load of less than 1000 copies per mL. In this interim analysis, safety and reactogenicity was assessed in all individuals who received at least one dose of ChAdOx1 nCov 19 between enrolment and Jan 15, 2021. Primary immunogenicity analyses included participants who received two doses of trial intervention and were SARS-CoV-2 seronegative at baseline. This trial is registered with ClinicalTrials.gov, NCT04444674, and the Pan African Clinicals Trials Registry, PACTR202006922165132.

Findings: Between June 24 and Nov 12, 2020, 104 people with HIV and 70 HIV-negative individuals were enrolled. 102 people with HIV (52 vaccine; 50 placebo) and 56 HIV-negative participants (28 vaccine; 28 placebo) received the priming dose, 100 people with HIV (51 vaccine; 49 placebo) and 46 HIV-negative participants (24 vaccine; 22 placebo) received two doses (priming and booster). In participants seronegative for SARS-CoV-2 at baseline, there were 164 adverse events in those with HIV (86 vaccine; 78 placebo) and 237 in HIV-negative participants (95 vaccine; 142 placebo). Of seven serious adverse events, one severe fever in a HIV-negative participant was definitely related to trial intervention and one severely elevated alanine aminotranferase in a

participant with HIV was unlikely related; five others were deemed unrelated. One person with HIV died (unlikely related). People with HIV and HIV-negative participants showed vaccine-induced serum IgG responses against wild-type Wuhan-1 Asp614Gly (also known as D614G). For participants seronegative for SARS-CoV-2 antigens at baseline, full-length spike geometric mean concentration (GMC) at day 28 was 163·7 binding antibody units (BAU)/mL (95% CI 89·9–298·1) for people with HIV (n=36) and 112·3 BAU/mL (61·7–204·4) for HIV-negative participants (n=23), with a rising day 42 GMC booster response in both groups. Baseline SARS-CoV-2 seropositive people with HIV demonstrated higher antibody responses after each vaccine dose than did people with HIV who were seronegative at baseline. High-level binding antibody cross-reactivity for the full-length spike and receptor-binding domain of the beta variant (B.1.351) was seen regardless of HIV status. In people with HIV who developed high titre responses, predominantly those who were receptor-binding domain seropositive at enrolment, neutralising activity against beta was retained.

Interpretation: ChAdOx1 nCoV-19 was well tolerated, showing favourable safety and immunogenicity in people with HIV, including heightened immunogenicity in SARS-CoV-2 baseline-seropositive participants. People with HIV showed cross-reactive binding antibodies to the beta variant and Asp614Gly wild-type, and high responders retained neutralisation against beta.

Reference

https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(21)00157-0/fulltext

The long-term sequelae of COVID-19: An international consensus on research priorities for patients with pre-existing and new-onset airways disease

Abstract

Persistent ill health after acute COVID-19—referred to as long COVID, the post-acute COVID-19 syndrome, or the post-COVID-19 condition—has emerged as a major concern. An international consensus exercise was undertook to identify research priorities with the aim of understanding the long-term effects of acute COVID-19, with a focus on people with pre-existing airways disease and the occurrence of new-onset airways disease and associated symptoms. 202 international experts were invited to submit a minimum of three research ideas. After a two-phase internal review process, a

final list of 98 research topics was scored by 48 experts. Patients with pre-existing or post-COVID-19 airways disease contributed to the exercise by weighting selected criteria. The highest-ranked research idea focused on investigation of the relationship between prognostic scores at hospital admission and morbidity at 3 months and 12 months after hospital discharge in patients with and without pre-existing airways disease. High priority was also assigned to comparisons of the prevalence and severity of post-COVID-19 fatigue, sarcopenia, anxiety, depression, and risk of future cardiovascular complications in patients with and without pre-existing airways disease. Our approach has enabled development of a set of priorities that could inform future research studies and funding decisions. This prioritisation process could also be adapted to other, non-respiratory aspects of long COVID.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00286-1/fulltext

Live imaging of SARS-CoV-2 infection in mice reveals that neutralizing antibodies require Fc function for optimal efficacy

Abstract

Neutralizing antibodies (NAbs) are effective in treating COVID-19, but the mechanism of immune protection is not fully understood. Here, live bioluminescence imaging (BLI) was applied to monitor the real-time effects of NAb treatment during prophylaxis and therapy of K18-hACE2 mice intranasally infected with SARS-CoV-2-nanoluciferase. Real-time imaging revealed that the virus spread sequentially from the nasal cavity to the lungs in mice and thereafter systemically to various organs including the brain, culminating in death. Highly potent NAbs from a COVID-19 convalescent subject prevented, and also effectively resolved, established infection when administered within three days. In addition to direct neutralization, depletion studies indicated that Fc effector interactions of NAbs with monocytes, neutrophils, and natural killer cells were required to effectively dampen inflammatory responses and limit immunopathology. The study highlights that both Fab and Fc effector functions of NAbs are essential for optimal *in vivo* efficacy against SARS-CoV-2.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00347-2

Vaccine nationalism and the dynamics and control of SARS-CoV-2

Abstract

Vaccines provide powerful tools to mitigate the enormous public health and economic costs that the ongoing SARS-CoV-2 pandemic continues to exert globally, yet vaccine distribution remains unequal among countries. To examine the potential epidemiological and evolutionary impacts of 'vaccine nationalism', previous models were extended to include simple scenarios of stockpiling between two regions. In general, when vaccines are widely available and the immunity they confer is robust, sharing doses minimizes total cases across regions. A number of subtleties arise when the populations and transmission rates in each region differ, depending on evolutionary assumptions and vaccine availability. When the waning of natural immunity contributes most to evolutionary potential, sustained transmission in low access regions results in an increased potential for antigenic evolution, which may result in the emergence of novel variants that affect epidemiological characteristics globally. Overall, our results stress the importance of rapid equitable vaccine distribution for global control of the pandemic.

Reference

https://www.science.org/doi/10.1126/science.abj7364

Publication Date: Aug 16, 2021

Distinguishing features of current COVID-19 vaccines: Knowns and unknowns of antigen presentation and modes of action

Abstract

COVID-19 vaccines were developed with an unprecedented pace since the beginning of the pandemic. Several of them have reached market authorization and mass production, leading to their global application on a large scale. This enormous progress was achieved with fundamentally different vaccine technologies used in parallel. mRNA, adenoviral vector as well as inactivated whole-virus vaccines are now in widespread use, and a subunit vaccine is in a final stage of authorization. They all rely on the native

viral spike protein (S) of SARS-CoV-2 for inducing potently neutralizing antibodies, but the presentation of this key antigen to the immune system differs substantially between the different categories of vaccines. In this article, it was reviewed that the relevance of structural modifications of S in different vaccines and the different modes of antigen expression after vaccination with genetic adenovirus-vector and mRNA vaccines. Distinguishing characteristics and unknown features are highlighted in the context of protective antibody responses and reactogenicity of vaccines.

Reference

http://www.nature.com/articles/s41541-021-00369-6

A particle swarm optimization approach for predicting the number of COVID-19 deaths

Abstract

The rapid spread of the COVID-19 pandemic has raised huge concerns about the prospect of a major health disaster that would result in a huge number of deaths. This anxiety was largely fueled by the fact that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the disease, was so far unknown, and therefore an accurate prediction of the number of deaths was particularly difficult. However, this prediction is of the utmost importance for public health authorities to make the most reliable decisions and establish the necessary precautions to protect people's lives. In this paper, an approach was presented for predicting the number of deaths from COVID-19. This approach requires modeling the number of infected cases using a generalized logistic function and using this function for inferring the number of deaths. An estimate of the parameters of the proposed model is obtained using a Particle Swarm Optimization algorithm (PSO) that requires iteratively solving a quadratic programming problem. In addition to the total number of deaths and number of infected cases, the model enables the estimation of the infection fatality rate (IFR). Furthermore, using some mild assumptions, we derive estimates of the number of active cases. The proposed approach was empirically assessed on official data provided by the State of Qatar. The results of the computational study show a good accuracy of the predicted number of deaths.

Reference

https://www.nature.com/articles/s41598-021-96057-5

SARS-CoV-2 variant prediction and antiviral drug design are enabled by RBD *in vitro* evolution

Abstract

SARS-CoV-2 variants of interest and concern will continue to emerge for the duration of the COVID-19 pandemic. To map mutations in the receptor-binding domain (RBD) of the spike protein that affect binding to angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, applied *in vitro* evolution to affinity-mature the RBD. Multiple rounds of random mutagenic libraries of the RBD were sorted against decreasing concentrations of ACE2, resulting in the selection of higher affinity RBD binders. It was found that mutations present in more transmissible viruses (S477N, E484K and N501Y) were preferentially selected in the high-throughput screen. Evolved RBD mutants include prominently the amino acid substitutions found in the RBDs of B.1.620, B.1.1.7 (Alpha), B1.351 (Beta) and P.1 (Gamma) variants. Moreover, the incidence of RBD mutations in the population as presented in the GISAID database (April 2021) is positively correlated with increased binding affinity to ACE2. Further *in vitro* evolution increased binding by 1,000-fold and identified mutations that may be more infectious if they evolve in the circulating viral population, for example, Q498R is epistatic to N501Y. It was shown that the high-affinity variant RBD-62 can be used as a drug to inhibit infection with SARS-CoV-2 and variants Alpha, Beta and Gamma *in vitro*. In a model of SARS-CoV-2 challenge in hamster, RBD-62 significantly reduced clinical disease when administered before or after infection. A 2.9 Å cryo-electron microscopy structure of the high-affinity complex of RBD-62 and ACE2, including all rapidly spreading mutations, provides a structural basis for future drug and vaccine development and for in silico evaluation of known antibodies.

Reference

https://www.nature.com/articles/s41564-021-00954-4

Safety and humoral responses to BNT162b2 mRNA vaccination of SARS-CoV-2 previously infected and naive populations

Abstract

Since COVID-19 risk of reinfection is of great concern, the safety and efficacy of the mRNA-based vaccines in previously infected populations should be assessed. 78 Individuals previously infected with SARS-CoV-19 were studied, who received a single dose of BNT162b2 mRNA COVID-19 vaccine, and 1:2 ratio matched infection-naïve cohort who received two injections. The evaluation procedure included symptom monitoring, and serological tests. Among the post-infected population, the median IgG-S response after the first vaccine dose was 3.35 AU, compared to 2.38 AU after the second vaccine injection in the infection naive group. A strong correlation was demonstrated between IgG-S level before vaccination, and the corresponding responses after a single vaccine dose ($r = 0.8$, $p < 0.001$) in the post infected population. Short-term severe symptoms that required medical attention were found in 6.8% among the post-infected individuals, while none were found in the infection naïve population. The data suggest that a single vaccine dose is sufficient to induce an intense immune response in post-infected population regardless of seropositivity. Although some short-term safety issues were observed compared to the infection naïve population, a single dose regimen can be considered safe in post-infected populations.

Reference

https://www.nature.com/articles/s41598-021-96129-6

Discovery and validation of a three-gene signature to distinguish COVID-19 and other viral infections in emergency infectious disease presentations: A case-control and observational cohort study

Abstract

Background: Emergency admissions for infection often lack initial diagnostic certainty. COVID-19 has highlighted a need for novel diagnostic approaches to indicate likelihood of viral infection in a pandemic setting. It was aimed to derive and validate a blood transcriptional signature to detect viral infections, including COVID-19, among adults with suspected infection who presented to the emergency department.

Methods: Individuals (aged ≥18 years) presenting with suspected infection to an emergency department at a major teaching hospital in the UK were prospectively recruited as part of the Bioresource in Adult Infectious Diseases (BioAID) discovery cohort. Whole-blood RNA sequencing was done on samples from participants with subsequently confirmed viral, bacterial, or no infection diagnoses. Differentially expressed host genes that met additional filtering criteria were subjected to feature selection to derive the most parsimonious discriminating signature. The signature was validated *via* RT-qPCR in a prospective validation cohort of participants who presented to an emergency department with undifferentiated fever, and a second case-control validation cohort of emergency department participants with PCR-positive COVID-19 or bacterial infection. Signature performance was assessed by calculating the area under receiver operating characteristic curves (AUROCs), sensitivities, and specificities.

Findings: A three-gene transcript signature, comprising HERC6, IGF1R, and NAGK, was derived from the discovery cohort of 56 participants with bacterial infections and 27 with viral infections. In the validation cohort of 200 participants, the signature differentiated bacterial from viral infections with an AUROC of 0·976 (95% CI 0·919−1·000), sensitivity of 97·3% (85·8−99·9), and specificity of 100% (63·1−100). The AUROC for C-reactive protein (CRP) was 0·833 (0·694−0·944) and for leukocyte count was 0·938 (0·840−0·986). The signature achieved higher net benefit in decision curve analysis than either CRP or leukocyte count for discriminating viral infections from all other infections. In the second validation analysis, which included SARS-CoV-2-positive participants, the signature discriminated 35 bacterial infections from 34 SARS-CoV-2-positive COVID-19 infections with AUROC of 0·953 (0·893−0·992), sensitivity 88·6%, and specificity of 94·1%.

Interpretation: This novel three-gene signature discriminates viral infections, including COVID-19, from other emergency infection presentations in adults, outperforming both leukocyte count and CRP, thus potentially providing substantial clinical utility in managing acute presentations with infection.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00145-2/fulltext

Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: A case series and nested case-control study

Abstract

Background: Bell's palsy is a rare adverse event reported in clinical trials of COVID-19 vaccines. However, to the knowledge no population-based study has assessed the association between the inactivated SARS-CoV-2 vaccines and Bell's palsy. The aim of this study was to evaluate the risk of Bell's palsy after BNT162b2 and CoronaVac vaccination.

Methods: In this case series and nested case-control study done in Hong Kong, we assessed the risk of Bell's palsy within 42 days following vaccination with BNT162b2 (Fosun–BioNTech [equivalent to Pfizer–BioNTech]) or CoronaVac (from Sinovac Biotech, Hong Kong) using data from voluntary surveillance reporting with the Hospital Authority, the COVID-19 Vaccine Adverse Event Online Reporting system for all health-care professionals, and the Hospital Authority's territory-wide electronic health records from the Clinical Data Analysis and Reporting System. We described reported cases of Bell's palsy among vaccine recipients (aged 18–110 years for CoronaVac and aged 16–110 years for BNT162b2). The estimated age-standardised incidence of clinically confirmed cases was compared among individuals who had received the CoronaVac or BNT162b2 vaccination (up to 42 days before presentation) with the background incidence in the population. A nested case-control study was also done using conditional logistic regression to estimate the odds ratio (OR) for risk of Bell's palsy and vaccination. Cases and controls were matched (1:4) by age, sex, admission setting, and admission date.

Findings: Between February 23 and May 4, 2021, 451 939 individuals received the first dose of CoronaVac and 537 205 individuals received the first dose of BNT162b2. 28 clinically confirmed cases of Bell's palsy were reported following CoronaVac and 16 cases were reported following BNT162b2. The age-standardised incidence of clinically confirmed Bell's palsy was 66·9 cases per 100 000 person-years (95% CI 37·2 to 96·6) following CoronaVac vaccination and 42·8 per 100 000 person-years (19·4 to 66·1) for BNT162b2 vaccination. The age-standardised difference for the incidence compared with the background population was 41·5 (95% CI 11·7 to 71·4) for CoronaVac and

17·0 (−6·6 to 40·6) for BNT162b2, equivalent to an additional 4·8 cases per 100 000 people vaccinated for CoronaVac and 2·0 cases per 100 000 people vaccinated for BNT162b2. In the nested case-control analysis, 298 cases were matched to 1181 controls, and the adjusted ORs were 2·385 (95% CI 1·415 to 4·022) for CoronaVac and 1·755 (0·886 to 3·477) for BNT162b2.

Interpretation: The findings suggested an overall increased risk of Bell's palsy after CoronaVac vaccination. However, the beneficial and protective effects of the inactivated COVID-19 vaccine far outweigh the risk of this generally self-limiting adverse event. Additional studies are needed in other regions to confirm our findings.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00451-5/fulltext

Near-physiological-temperature serial crystallography reveals conformations of SARS-CoV-2 main protease active site for improved drug repurposing

Abstract

The COVID-19 pandemic has resulted in 198 million reported infections and more than 4 million deaths as of July 2021 (covid19.who.int). Research to identify effective therapies for COVID-19 includes: (1) designing a vaccine as future protection; (2) de novo drug discovery; and (3) identifying existing drugs to repurpose them as effective and immediate treatments. To assist in drug repurposing and design, two apo structures of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease were determined at ambient temperature by serial femtosecond X-ray crystallography. We employ detailed molecular simulations of selected known main protease inhibitors with the structures and compare binding modes and energies. The combined structural and molecular modeling studies not only reveal the dynamics of small molecules targeting the main protease but also provide invaluable opportunities for drug repurposing and structure-based drug design strategies against SARS-CoV-2.

Reference

https://www.cell.com/structure/fulltext/S0969-2126(21)00257-4

A vaccine-induced public antibody protects against SARS-CoV-2 and emerging variants

Abstract

The emergence of SARS-CoV-2 antigenic variants with increased transmissibility is a public health threat. Some variants show substantial resistance to neutralization by SARS-CoV-2 infection- or vaccination-induced antibodies. Here, receptor binding domain-binding monoclonal antibodies derived from SARS-CoV-2 mRNA vaccine-elicited germinal center B cells were analyzed for neutralizing activity against the WA1/2020 D614G SARS-CoV-2 strain and variants of concern. Of five monoclonal antibodies that potently neutralized the WA1/2020 D614G strain, all retained neutralizing capacity against the B.1.617.2 variant, four also neutralized the B.1.1.7 variant, and only one, 2C08, also neutralized the B.1.351 and B.1.1.28 variants. 2C08 reduced lung viral load and morbidity in hamsters challenged with the WA1/2020 D614G, B.1.351, or B.1.617.2 strains. Clonal analysis identified 2C08-like public clonotypes among B cells responding to SARS-CoV-2 infection or vaccination in 41 out of 181 individuals. Thus, 2C08-like antibodies can be induced by SARS-CoV-2 vaccines and mitigate resistance by circulating variants of concern.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00345-9

The nucleotide addition cycle of the SARS-CoV-2 polymerase

Abstract

Coronaviruses have evolved elaborate multisubunit machines to replicate and transcribe their genomes. Central to these machines are the RNA-dependent RNA polymerase subunit (nsp12) and its intimately associated cofactors (nsp7 and nsp8). A high-throughput magnetic-tweezers approach was used to develop a mechanochemical description of this core polymerase. The core polymerase exists in at least three catalytically distinct conformations, one being kinetically consistent with incorporation of incorrect nucleotides. Evidence was provided that the RNA-dependent RNA polymerase (RdRp) uses a thermal ratchet instead of a power stroke to transition from the pre- to post-translocated state. Ultra-stable magnetic tweezers enable the direct observation of

coronavirus polymerase deep and long-lived backtracking that is strongly stimulated by secondary structures in the template. The framework we present here elucidates one of the most important structure-dynamics-function relationships in human health today and will form the grounds for understanding the regulation of this complex.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01093-7

Generation and transmission of inter-lineage recombinants in the SARS-CoV-2 pandemic

Abstract

Evidence for multiple independent origins of recombinant SARS-CoV-2 viruses sampled from late 2020 and early 2021 in the United Kingdom, were presented. Their genomes carry single nucleotide polymorphisms and deletions that are characteristic of the B.1.1.7 variant of concern, but lack the full complement of lineage-defining mutations. Instead, the remainder of their genomes shared contiguous genetic variation with non-B.1.1.7 viruses circulating in the same geographic area at the same time as the recombinants. In four instances there was evidence for onward transmission of a recombinant-origin virus, including one transmission cluster of 45 sequenced cases over the course of two months. The inferred genomic locations of recombination breakpoints suggest that every community-transmitted recombinant virus inherited its spike region from a B.1.1.7 parental virus, consistent with a transmission advantage for B.1.1.7's set of mutations.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00984-3

Prioritizing vaccination by age and social activity to advance societal health benefits in Norway: A modelling study

Abstract

Background: Vaccination has the proven effectiveness in reducing disease burden. As the emergency program is moving towards completion in many countries, there is a new urgency to appropriately assess the societal health benefits in both the near and longer term.

Methods: Using an age-structured mathematical infection model, the gains achievable by adopting the ongoing and the possible alternative vaccination strategies were evaluated to reduce COVID-19 infections in the current pandemic as well as during the future successive waves in Norway. Three allocation strategies were explicitly considered, with single focus group on either (i) the older age groups at high risk of dying or (ii) the core-sociable groups at high risk of exposure and onwards transmission, versus strategies focusing on both groups by (iii) switching among the high-risk to the core-sociable.

Findings: Following the Norwegian Institute of Public Health (FHI) schedule, it was estimated that allocating vaccines in an age-descending order may reduce around one-third of the infections; while strategy considering age-specific sociability may contribute to an additional ~10% fewer infections.

Interpretation: A key insight of the study is that prioritizing the high-risk and core-sociable groups may maximize the benefit due to both direct and indirect protections, and thus achieving the larger societal health benefits. The analyses provide a quantitative tool to planning of future campaigns for Scandinavian and other countries with comparable infection-fatality ratios, demographies and public health infrastructure.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00177-0/fulltext

Safety and immunogenicity of a QazCovid-in® inactivated whole-virion vaccine against COVID-19 in healthy adults: A single-centre, randomised, single-blind, placebo-controlled phase 1 and an open-label phase 2 clinical trials with a 6 months follow-up in Kazakhstan

Abstract

Background: A new inactivated whole-virion QazCovid-in® vaccine against COVID-19 was developed from SARS-CoV-2 isolated in Kazakhstan, inactivated by formaldehyde, and adjuvanted with aluminium hydroxide. Phase 1 and 2 clinical trials aimed at assessing the vaccine's safety, immunogenicity, and the duration of immunity induced by the QazCovid-in® vaccine after one or two immunisations.

Methods: From 23.09.2020 to 19.03.2021 we performed a randomised, single-blind, placebo-controlled phase 1 clinical trial and from 18.10.2020 to 17.04.2021 an open-label phase 2 clinical trials of the QazCovid-in® vaccine with a 6 months follow-up at a single centre in Almaty, the Republic of Kazakhstan. Eligible healthy adults aged 18 years and older with no history of laboratory-confirmed SARS-CoV-2 infection were randomly assigned to the treatment groups using a computerised randomisation scheme generator. In the phase 1 clinical trial, two doses of the vaccine (5 μg each) or placebo (0·9% NaCl) were administered intramuscularly to 44 subjects aged 18–50 years, 21 days apart. In the phase 2 trial, 200 healthy participants were randomised into four equal-sized groups according to the age (18–49 or ≥50 years) and either single (day 1) or double (day 1 and 21) vaccination protocol. The primary outcomes were safety and tolerability. The secondary outcome was immunogenicity. The cellular response was measured by a whole-blood cytokine release assay (phase 1 only). The trials were registered with ClinicalTrials.gov NCT04530357.

Findings: The QazCovid-in® vaccine was safe and well-tolerated and induced predominantly mild adverse events; no serious or severe adverse events were recorded in both trials. In the phase 1 trial, the percentage of subjects with a fourfold increase of antibody titres (sero conversion) in MNA was 59% after one vaccine dose and amounted to 100% after two doses. Neutralizing antibody titres reached the geometric mean titre (GMT) of 100 after administration of two doses. A statistically significant

increase in the levels of pro-inflammatory cytokines after vaccination indicated the Th1-biased response. On day 180, 40% of placebo-treated subjects demonstrated a statistically significant increase in the levels of antibodies measured by both ELISA and MNA, which suggests the infection with SARS-CoV-2. In the phase 2 trial, 100% of subjects aged 18–49 years seroconverted for SARS-CoV-2 on day 21 after the first dose, as indicated by MNA yielding the GMTs of 32 or 30 in the one- and two-dose groups, respectively. Amongst ≥50-year-old subjects, the number of sero conversions in the two- and one-dose groups on day 21 was 94% and 92% with the respective GMTs of 25 and 24. After the second dose, the sero conversion rate reached 100%; however, the GMT was significantly lower when compared with the corresponding value measured in subjects aged 18–49 years (83 vs 143). In both trials, specific antibodies were detected in MNA and ELISA on study day 180, but the titres dropped in comparison to day 42. The results of this study serve as the rationale for the phase 3 study.

Interpretation: The QazCovid-in® vaccine is safe and well-tolerated and promotes pronounced humoral immunity which lasts for at least 6 months after double intramuscular immunisation.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00358-8/fulltext

Protective heterologous T cell immunity in COVID-19 induced by the trivalent Measles-Mumps-Rubella and Tetanus-Diptheria-Pertussis vaccine antigens

Abstract

Background: T cells control viral infection and promote vaccine durability and in COVID-19 associate with mild disease. It was investigated whether prior Measles-Mumps-Rubella (MMR) or Tetanus-Diptheria-Pertussis (Tdap) vaccination elicit cross-reactive T cells that mitigate COVID-19.

Methods: Antigen presenting cells (APC) loaded ex vivo with SARS-CoV-2, MMR or Tdap antigens and autologous T cells from COVID-19 convalescent and uninfected individuals, and COVID-19 mRNA vaccinated donors were co-cultured and T cell activation and phenotype were detected by IFN-γ ELISpot assays and flow cytometry.

ELISA assays and validation studies identified the APC-derived cytokine(s) driving T cell activation. TCR clonotyping and scRNA-seq identified cross-reactive T cells and their transcriptional profile. A propensity-weighted analysis of COVID-19 patients estimated the effects of MMR and Tdap vaccination on COVID-19 outcomes.

Findings: High correlation was observed between T cell responses to SARS-CoV-2 (Spike-S1 and Nucleocapsid) and MMR and Tdap proteins in COVID-19 convalescent and vaccinated individuals. The overlapping T cell population contained an effector memory T cell subset (TEMRA) implicated in protective, anti-viral immunity and their detection required APC-derived IL-15, known to sensitize T cells to activation. Cross-reactive TCR repertoires detected in antigen-experienced T cells recognizing SARS-CoV-2, MMR and Tdap epitopes had TEMRA features. Indices of disease severity were reduced in MMR or Tdap vaccinated individuals by 32-38% and 20-23% respectively, among COVID-19 patients.

Conclusions: Tdap and MMR memory T cells reactivated by SARS-CoV-2 may provide protection against severe COVID-19 disease.

Reference

https://www.cell.com/med/fulltext/S2666-6340(21)00289-0

A monocyte/dendritic cell molecular signature of SARS-CoV-2-related multisystem inflammatory syndrome in children with severe myocarditis

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children is generally milder than in adults, but a proportion of cases result in hyperinflammatory conditions often including myocarditis.

Methods: To better understand these cases, a multiparametric approach was applied to the study of blood cells of 56 children hospitalized with suspicion of SARS-CoV-2 infection. Plasma cytokine and chemokine levels and blood cellular composition were measured, alongside gene expression at the bulk and single-cell levels.

Findings: The most severe forms of multisystem inflammatory syndrome in children (MIS-C) related to SARS-CoV-2 that resulted in myocarditis were characterized by elevated levels of pro-angiogenesis cytokines and several chemokines. Single-cell

transcriptomics analyses identified a unique monocyte/dendritic cell gene signature that correlated with the occurrence of severe myocarditis characterized by sustained nuclear factor κB (NF-κB) activity and tumor necrosis factor alpha (TNF-α) signaling and associated with decreased gene expression of NF-κB inhibitors. We also found a weak response to type I and type II interferons, hyperinflammation, and response to oxidative stress related to increased HIF-1α and Vascular endothelial growth factor (VEGF) signaling.

Conclusions: These results provide potential for a better understanding of disease pathophysiology.

Reference

https://www.cell.com/med/fulltext/S2666-6340(21)00287-7

Ultrapotent antibodies against diverse and highly transmissible SARS-CoV-2 variants

Abstract

The emergence of highly transmissible SARS-CoV-2 variants of concern (VOCs) that are resistant to therapeutic antibodies highlights the need for continuing discovery of broadly reactive antibodies. Four receptor binding domain–targeting antibodies were identified from three early-outbreak convalescent donors with potent neutralizing activity against 23 variants, including the B.1.1.7, B.1.351, P.1, B.1.429, B.1.526, and B.1.617 VOCs. Two antibodies are ultrapotent, with subnanomolar neutralization titers [half-maximal inhibitory concentration (IC_{50}) 0.3 to 11.1 nanograms per milliliter; IC_{80} 1.5 to 34.5 nanograms per milliliter). The structural and functional determinants of binding were defined for all four VOC-targeting antibodies and show that combinations of two antibodies decrease the *in vitro* generation of escape mutants, suggesting their potential in mitigating resistance development.

Reference

https://www.science.org/doi/10.1126/science.abh1766

Effect of SARS-CoV-2 B.1.1.7 mutations on spike protein structure and function

Abstract

The B.1.1.7 variant of SARS-CoV-2 first detected in the UK harbors amino-acid substitutions and deletions in the spike protein that potentially enhance host angiotensin conversion enzyme 2 (ACE2) receptor binding and viral immune evasion. Here cryo-EM structures of the spike protein of B.1.1.7 were reported in the apo and ACE2-bound forms. The apo form showed one or two receptor-binding domains (RBDs) in the open conformation, without populating the fully closed state. All three RBDs were engaged in ACE2 binding. The B.1.1.7-specific A570D mutation introduces a molecular switch that could modulate the opening and closing of the RBD. The N501Y mutation introduces a *π*–*π* interaction that enhances RBD binding to ACE2 and abolishes binding of a potent neutralizing antibody (nAb). Cryo-EM also revealed how a cocktail of two nAbs simultaneously bind to all three RBDs, and demonstrated the potency of the nAb cocktail to neutralize different SARS-CoV-2 pseudovirus strains, including B.1.1.7.

Reference

https://www.nature.com/articles/s41594-021-00652-z

Potent prophylactic and therapeutic efficacy of recombinant human ACE2-Fc against SARS-CoV-2 infection *in vivo*

Abstract

The current COVID-19 pandemic, caused by SARS-CoV-2, poses a serious public health threat. Effective therapeutic and prophylactic treatments are urgently needed. Angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2, which binds to the receptor binding domain (RBD) of SARS-CoV-2 spike protein. Here, recombinant human ACE2-Fc fusion protein (hACE2-Fc) and a hACE2-Fc mutant with reduced catalytic activity, were developed. hACE2-Fc and the hACE2-Fc mutant both efficiently blocked entry of SARS-CoV-2, SARS-CoV, and HCoV-NL63 into hACE2-expressing cells and inhibited SARS-CoV-2 S protein-mediated cell–cell fusion. hACE2-Fc also neutralized various SARS-CoV-2 strains with enhanced infectivity including

D614G and V367F mutations, as well as the emerging SARS-CoV-2 variants, B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.1 (Kappa), and B.1.617.2 (Delta), demonstrating its potent and broad-spectrum antiviral effects. In addition, hACE2-Fc proteins protected HBE from SARS-CoV-2 infection. Unlike RBD-targeting neutralizing antibodies, hACE2-Fc treatment did not induce the development of escape mutants. Furthermore, both prophylactic and therapeutic hACE2-Fc treatments effectively protected mice from SARS-CoV-2 infection, as determined by reduced viral replication, weight loss, histological changes, and inflammation in the lungs. The protection provided by hACE2 showed obvious dose-dependent efficacy *in vivo*. Pharmacokinetic data indicated that hACE2-Fc has a relative long half-life *in vivo* compared to soluble ACE2, which makes it an excellent candidate for prophylaxis and therapy for COVID-19 as well as for SARS-CoV and HCoV-NL63 infections.

Reference

https://www.nature.com/articles/s41421-021-00302-0

A molecular test based on RT-LAMP for rapid, sensitive and inexpensive colorimetric detection of SARS-CoV-2 in clinical samples

Abstract

Until there is an effective implementation of COVID-19 vaccination program, a robust testing strategy, along with prevention measures, will continue to be the most viable way to control disease spread. Such a strategy should rely on disparate diagnostic tests to prevent a slowdown in testing due to lack of materials and reagents imposed by supply chain problems, which happened at the beginning of the pandemic. In this study, we have established a single-tube test based on RT-LAMP that enables the visual detection of less than 100 viral genome copies of SARS-CoV-2 within 30 min. The assay was benchmarked against the gold standard test for COVID-19 diagnosis, RT-PCR, using 177 nasopharyngeal RNA samples. For viral loads above 100 copies, the RT-LAMP assay had a sensitivity of 100% and a specificity of 96.1%. Additionally, we set up a RNA extraction-free RT-LAMP test capable of detecting SARS-CoV-2 directly from saliva samples, albeit with lower sensitivity. The saliva was self-collected and the collection tube remained closed until inactivation, thereby ensuring the protection of the testing personnel. As expected, RNA extraction from saliva samples increased the

sensitivity of the test. To lower the costs associated with RNA extraction, this step was performed using an alternative protocol that uses plasmid DNA extraction columns. The enzymes were also produced that were needed for the assay and established an in-house-made RT-LAMP test independent of specific distribution channels. Finally, a new colorimetric method was developed that allowed the detection of LAMP products by the visualization of an evident color shift, regardless of the reaction pH.

Reference

https://www.nature.com/articles/s41598-021-95799-6

The janus-kinase inhibitor ruxolitinib in SARS-CoV-2 induced acute respiratory distress syndrome (ARDS)

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 (coronavirus disease 2019), which is associated with high morbidity and mortality, especially in elder patients. Acute respiratory distress syndrome (ARDS) is a life-threatening complication of COVID-19 and has been linked with severe hyperinflammation. Dexamethasone has emerged as standard of care for COVID-19 associated respiratory failure. In a non-randomized prospective phase II multi-center study, we asked whether targeted inhibition of Janus kinase-mediated cytokine signaling using ruxolitinib is feasible and efficacious in SARS-CoV-2- induced ARDS with hyperinflammation. Sixteen SARS-CoV-2 infected patients requiring invasive mechanical ventilation for ARDS were treated with ruxolitinib in addition to standard treatment. Ruxolitinib treatment was well tolerated and 13 patients survived at least the first 28 days on treatment, which was the primary endpoint of the trial. Immediate start of ruxolitinib after deterioration was associated with improved outcome, as was a lymphocyte-to-neutrophils ratio above 0.07. Together, treatment with the janus-kinase inhibitor ruxolitinib is feasible and might be efficacious in COVID-19 induced ARDS patients requiring invasive mechanical ventilation. The trial has been registered under EudraCT-No.: 2020-001732-10 and NCT04359290.

Reference

https://www.nature.com/articles/s41375-021-01374-3

Looking for pathways related to COVID-19: Confirmation of pathogenic mechanisms by SARS-CoV-2–host interactome

Abstract

In the last months, many studies have clearly described several mechanisms of SARS-CoV-2 infection at cell and tissue level, but the mechanisms of interaction between host and SARS-CoV-2, determining the grade of COVID-19 severity, are still unknown. A network analysis was provided on protein–protein interactions (PPI) between viral and host proteins to better identify host biological responses, induced by both whole proteome of SARS-CoV-2 and specific viral proteins. A host-virus interactome was inferred, applying an explorative algorithm (Random Walk with Restart, RWR) triggered by 28 proteins of SARS-CoV-2. The analysis of PPI allowed to estimate the distribution of SARS-CoV-2 proteins in the host cell. Interactome built around one single viral protein allowed to define a different response, underlining as ORF8 and ORF3a modulated cardiovascular diseases and pro-inflammatory pathways, respectively. Finally, the network-based approach highlighted a possible direct action of ORF3a and NS7b to enhancing Bradykinin Storm. This network-based representation of SARS-CoV-2 infection could be a framework for pathogenic evaluation of specific clinical outcomes. We identified possible host responses induced by specific proteins of SARS-CoV-2, underlining the important role of specific viral accessory proteins in pathogenic phenotypes of severe COVID-19 patients.

Reference

https://www.nature.com/articles/s41419-021-03881-8

Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: A prospective cohort study

Abstract

Background: Heterologous vaccine regimens have been widely discussed as a way to mitigate intermittent supply shortages and to improve immunogenicity and safety of COVID-19 vaccines. It was aimed to assess the reactogenicity and immunogenicity of heterologous immunisations with ChAdOx1 nCov-19 (AstraZeneca, Cambridge, UK)

and BNT162b2 (Pfizer-BioNtech, Mainz, Germany) compared with homologous BNT162b2 and ChAdOx1 nCov-19 immunisation.

Methods: This is an interim analysis of a prospective observational cohort study enrolling health-care workers in Berlin (Germany) who received either homologous ChAdOx1 nCov-19 or heterologous ChAdOx1 nCov-19–BNT162b2 vaccination with a 10–12-week vaccine interval or homologous BNT162b2 vaccination with a 3-week vaccine interval. Reactogenicity was assessed after the first and second vaccination by use of electronic questionnaires on days 1, 3, 5, and 7. Immunogenicity was measured by the presence of SARS-CoV-2-specific antibodies (full spike-IgG, S1-IgG, and RBD-IgG), by an RBD–ACE2 binding inhibition assay (surrogate SARS-CoV-2 virus neutralisation test), a pseudovirus neutralisation assay against two variants of concerns (alpha [B.1.1.7] and beta [B.1.351]), and anti-S1-IgG avidity. T-cell reactivity was measured by IFN-γ release assay.

Findings: Between Dec 27, 2020, and June 14, 2021, 380 participants were enrolled in the study, with 174 receiving homologous BNT162b2 vaccination, 38 receiving homologous ChAdOx1 nCov-19 vaccination, and 104 receiving ChAdOx1 nCov-19–BNT162b2 vaccination. Systemic symptoms were reported by 103 (65%, 95% CI 57·1–71·8) of 159 recipients of homologous BNT162b2, 14 (39%, 24·8–55·1) of 36 recipients of homologous ChAdOx1 nCov-19, and 51 (49%, 39·6–58·5) of 104 recipients of ChAdOx1 nCov-19–BNT162b2 after the booster immunisation. Median anti-RBD IgG levels 3 weeks after boost immunisation were 5·4 signal to cutoff ratio (S/co; IQR 4·8–5·9) in recipients of homologous BNT162b2, 4·9 S/co (4·3–5·6) in recipients of homologous ChAdOx1 nCov-19, and 5·6 S/co (5·1–6·1) in recipients of ChAdOx1 nCov-19– BNT162b2. Geometric mean of 50% inhibitory dose against alpha and beta variants were highest in recipients of ChAdOx1 nCov-19–BNT162b2 (956·6, 95% CI 835·6–1095, against alpha and 417·1, 349·3–498·2, against beta) compared with those in recipients of homologous ChAdOx1 nCov-19 (212·5, 131·2–344·4, against alpha and 48·5, 28·4–82·8, against beta; both p<0·0001) or homologous BNT162b2 (369·2, 310·7–438·6, against alpha and 72·4, 60·5–86·5, against beta; both p<0·0001). SARS-CoV-2 S1 T-cell reactivity 3 weeks after boost immunisation was highest in recipients of ChAdOx1 nCov-19–BNT162b2 (median IFN-γ concentration 4762 mIU/mL, IQR 2723–8403) compared with that in recipients of homologous ChAdOx1 nCov-19 (1061

mIU/mL, 599–2274, p<0·0001) and homologous BNT162b2 (2026 mIU/mL, 1459–4621, p=0·0008) vaccination.

Interpretation: The heterologous ChAdOx1 nCov-19–BNT162b2 immunisation with 10–12-week interval, recommended in Germany, is well tolerated and improves immunogenicity compared with homologous ChAdOx1 nCov-19 vaccination with 10–12-week interval and BNT162b2 vaccination with 3-week interval. Heterologous prime-boost immunisation strategies for COVID-19 might be generally applicable.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00357-X/fulltext

Phase I dose-escalation single centre clinical trial to evaluate the safety of infusion of memory T cells as adoptive therapy in COVID-19 (RELEASE)

Abstract

Background: Effective treatments are still needed to reduce the severity of symptoms, time of hospitalization, and mortality of COVID-19. SARS-CoV-2 specific memory T-lymphocytes obtained from convalescent donors recovered can be used as passive cell immunotherapy.

Methods: Between September and November 2020 a phase 1, dose-escalation, single centre clinical trial was conducted to evaluate the safety and feasibility of the infusion of CD45RA− memory T cells containing SARS-CoV-2 specific T cells as adoptive cell therapy against moderate/severe cases of COVID-19. Nine participants with pneumonia and/or lymphopenia and with at least one human leukocyte antigen (HLA) match with the donor were infused. The first three subjects received the lowest dose (1 × 105 cells/kg), the next three received the intermediate dose (5 × 105 cells/kg) and the last three received the highest dose (1 × 106 cells/kg) of CD45RA− memory T cells. Clinicaltrials.gov registration: NCT04578210.

Findings: All participants' clinical status measured by National Early Warning Score (NEWS) and 7-category point ordinal scales showed improvement six days after infusion. No serious adverse events were reported. Inflammatory parameters were stabilised post-infusion and the participants showed lymphocyte recovery two weeks

after the procedure. Donor microchimerism was observed at least for three weeks after infusion in all patients.

Interpretation: This study provides preliminary evidence supporting the idea that treatment of COVID-19 patients with moderate/severe symptoms using convalescent CD45RA− memory T cells is feasible and safe.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00366-7/fulltext

COVID-19 and the effects on pulmonary function following infection: A retrospective analysis

Abstract

Background: The coronavirus disease 2019 (COVID-19) has been identified in over 110 million people with no studies comparing pre-infection pulmonary function to post-infection. This study's aim was to compare pre-infection and post-infection pulmonary function tests (PFT) in COVID-19 infected patients to better delineate between preexisting abnormalities and effects of the virus.

Methods: This was a retrospective multi-center cohort study. Patients were identified based on having COVID-19 and a pre- and post-infection PFT within one year of infection during the time period of March 1, 2020 to November 10, 2020.

Findings: There was a total of 80 patients, with an even split in gender; the majority were white (n = 70, 87·5%) and never smokers (n = 42, 52·5%). The majority had mild to moderate COVID-19 disease (n = 60, 75·1%) with 25 (31·2%) requiring hospitalization. There was no difference between the pre- and post-PFT data, specifically with the forced vital capacity (FVC) (p = 0·52), forced expiratory volume in 1 s (FEV1)(p = 0·96), FEV1/FVC(p = 0·66), total lung capacity (TLC) (p = 0·21), and diffusion capacity (DLCO)(p = 0·88). There was no difference in the PFT when analyzed by hospitalization and disease severity. After adjusting for potential confounders, interstitial lung disease (ILD) was independently associated with a decreased FEV1 (-2·6 [95% CI, -6·7 to - 1·6] vs. -10·3 [95% CI, -17·7 to -2·9]; p = 0·03) and an increasing age (p = 0·01) and cystic fibrosis (-1·1 [95% CI, -4·5 to- 2·4] vs. -36·5 [95% CI, -52·1 to -21·0]; p < 0·01) were associated with decreasing FVC when comparing pre and post infection PFT. Only

increasing age was independently associated with a reduction in TLC ($p = 0{\cdot}01$) and DLCO ($p = 0{\cdot}02$) before and after infection.

Interpretation: This study showed that there is no difference in pulmonary function as measured by PFT before and after COVID-19 infection in non-critically ill classified patients. There could be a relationship with certain underlying lung diseases (interstitial lung disease and cystic fibrosis) and decreased lung function following infection. This information should aid clinicians in their interpretation of pulmonary function tests obtained following COVID-19 infection.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00359-X/fulltext

The importation and establishment of community transmission of SARS-CoV-2 during the first eight weeks of the South African COVID-19 epidemic

Abstract

Background: The epidemiology of COVID-19 in South Africa was described following importation and during implementation of stringent lockdown measures.

Methods: Using national surveillance data including demographics, laboratory test data, clinical presentation, risk exposures (travel history, contacts and occupation) and outcomes of persons undergoing COVID-19 testing or hospitalised with COVID-19 at sentinel surveillance sites, descriptive statistics, epidemic curves, and initial reproductive numbers (Rt) were generated and interpreted.

Findings: From 4 March to 30 April 2020, 271,670 SARS-CoV-2 PCR tests were performed (462 tests/100,000 persons). Of these, 7,892 (2.9%) persons tested positive (median age 37 years (interquartile range 28–49 years), 4,568 (58%) male, cumulative incidence of 13.4 cases/100,000 persons). Hospitalization records were found for 1,271 patients (692 females (54%)) of whom 186 (14.6%) died. Amongst 2,819 cases with data, 489/2819 (17.3%) travelled internationally within 14 days prior to diagnosis, mostly during March 2020 (466 (95%)). Cases diagnosed in April compared with March were younger (median age, 37 vs. 40 years), less likely female (38% vs. 53%) and resident in a more populous province (98% vs. 91%). The national initial Rt was 2.08 (95% confidence interval (CI): 1.71–2.51).

Interpretation: The first eight weeks following COVID-19 importation were characterised by early predominance of imported cases and relatively low mortality and transmission rates. Despite stringent lockdown measures, the second month following importation was characterized by community transmission and increasing disease burden in more populous provinces.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00352-7/fulltext

Antiphospholipid antibodies and neurological manifestations in acute COVID-19: A single-centre cross-sectional study

Abstract

Background: A high prevalence of antiphospholipid antibodies has been reported in case series of patients with neurological manifestations and COVID-19; however, the pathogenicity of antiphospholipid antibodies in COVID-19 neurology remains unclear.

Methods: This single-centre cross-sectional study included 106 adult patients: 30 hospitalised COVID-neurological cases, 47 non-neurological COVID-hospitalised controls, and 29 COVID-non-hospitalised controls, recruited between March and July 2020. We evaluated nine antiphospholipid antibodies: anticardiolipin antibodies [aCL] IgA, IgM, IgG; anti-beta-2 glycoprotein-1 [aβ2GPI] IgA, IgM, IgG; anti-phosphatidylserine/prothrombin [aPS/PT] IgM, IgG; and anti-domain I β2GPI (aD1β2GPI) IgG.

Findings: There was a high prevalence of antiphospholipid antibodies in the COVID-neurological (73.3%) and non-neurological COVID-hospitalised controls (76.6%) in contrast to the COVID-non-hospitalised controls (48.2%). aPS/PT IgG titres were significantly higher in the COVID-neurological group compared to both control groups ($p < 0.001$). Moderate-high titre of aPS/PT IgG was found in 2 out of 3 (67%) patients with acute disseminated encephalomyelitis [ADEM]. aPS/PT IgG titres negatively correlated with oxygen requirement (FiO2 $R=-0.15$ $p = 0.040$) and was associated with venous thromboembolism ($p = 0.043$). In contrast, aCL IgA ($p < 0.001$) and IgG ($p < 0.001$) was associated with non-neurological COVID-hospitalized controls compared to the other groups and correlated positively with d-dimer and creatinine but negatively with FiO_2.

Interpretation: The findings show that aPS/PT IgG is associated with COVID-19-associated ADEM. In contrast, aCL IgA and IgG are seen much more frequently in non-neurological hospitalized patients with COVID-19. Characterization of antiphospholipid antibody persistence and potential longitudinal clinical impact are required to guide appropriate management.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00350-3/fulltext

Rapid induction of antigen-specific $CD4^+$ T cells is associated with coordinated humoral and cellular immunity to SARS-CoV-2 mRNA vaccination

Abstract

SARS-CoV-2 mRNA vaccines have shown remarkable clinical efficacy, but questions remain about the nature and kinetics of T cell priming. Longitudinal antigen-specific T cell analyses were performed on healthy SARS-CoV-2-naive and recovered individuals prior to and following mRNA prime and boost vaccination. Vaccination induced rapid antigen-specific $CD4^+$ T cell responses in naive subjects after the first dose, whereas $CD8^+$ T cell responses developed gradually and were variable in magnitude. Vaccine-induced Th1 and Tfh cell responses following the first dose correlated with post-boost $CD8^+$ T cells and neutralizing antibodies, respectively. Integrated analysis revealed coordinated immune responses with distinct trajectories in SARS-CoV-2-naive and recovered individuals. Last, whereas booster vaccination improved T cell responses in SARS-CoV-2-naive subjects, the second dose had little effect in SARS-CoV-2-recovered individuals. These findings highlight the role of rapidly primed $CD4^+$ T cells in coordinating responses to the second vaccine dose in SARS-CoV-2-naive individuals.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00308-3

CORRESPONDANCE

Publication Date: Aug 17, 2021

SARS-CoV-2 delta variant neutralization after heterologous ChAdOx1-S/BNT162b2 vaccination

Safety considerations associated with the Oxford–AstraZeneca COVID-19 ChAdOx1-S vaccine (AZD1222) have led many public health agencies to recommend a heterologous boost with an mRNA vaccine after prime vaccination with ChAdOx1-S instead of a homologous boost. The first results of a phase 2 trial from Spain1 and additional reports from observational studies suggest robust immune responses accompanied by acceptable reactogenicity after ChAdOx1-S prime and BNT162b22, 3 (Pfizer–BioNTech) or mRNA-12734 (Moderna) boost vaccination. Given the strong immune response after heterologous prime-boost vaccination, mixing of vaccines has been suggested as a suitable strategy to contain emerging SARS-CoV-2 variants.5

Heterologous boosting with BNT162b2 has been shown to induce higher counts of spike-specific $CD4^+$ and $CD8^+$ T cells and, in particular, high titres of neutralising antibodies in a surrogate test against the SARS-CoV-2 variants of concern (VOCs) alpha, beta, and gamma.3 However, the rapid spread of the delta variant is a concern for both ChAdOx1-S-primed vaccines who are expecting a boost vaccination and for individuals who have been fully vaccinated with ChAdOx1-S. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01891-2/fulltext

Publication Date: Aug 13, 2021

Rapid genome sequencing in hospitals to identify potential vaccine-escape SARS-CoV-2 variants

SARS-CoV-2 genome sequencing is embedded in academic and public health laboratories, but whether there are benefits to rapid sequencing in front-line hospital laboratories is unclear. A rapid genome sequencing of SARS-CoV-2-positive nose and

throat swabs was done from patients admitted to our hospital since July 7, 2021, to identify potential SARS-CoV-2 vaccine-escape variants for infection control and public health purposes. In addition, PCR-based genotyping of all new SARS-CoV-2 cases was done for three south London hospitals (Guy's and St Thomas', King's College, and Princess Royal University) using the AusDiagnostics SARS-CoV-2 Typing Panel (16-well) on the AusDiagnostics HighPlex, sequencing any non-typeable results.

Two cases of a potential vaccine-escape variant from the B.1.621 lineage were identified. This variant of interest, first identified in Colombia, has lineage-associated spike mutations R346K, E484K, and P681H, which have been reported to show reduced neutralisation by antibodies. In addition, the variant we detected harbours a K417N spike mutation, which is associated with vaccine escape in the beta variant first identified in South Africa. This variant was first identified on July 12, 2021, and since then more cases have been reported by public health authorities. The presence of mutations associated with vaccine escape might warrant reclassification of this variant to a variant of concern and deployment of additional public health resources to contain spread. For more details, read the link below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00482-5/fulltext

Publication Date: Aug 12, 2021

Neutralising antibodies after COVID-19 vaccination in UK haemodialysis patients

Vaccination against COVID-19 induces highly protective immune responses in most people. As some countries switch from suppression to acceptance of transmission of SARS-CoV-2 within a largely vaccinated adult population, vulnerable patient groups that have not mounted adequate immune responses to vaccination might experience significant morbidity and mortality. There is an urgent need to identify such patient groups and to optimise medical advice and vaccination strategies for them. In-centre haemodialysis patients are a particularly vulnerable group. During the first wave of the COVID-19 pandemic (March 1 to Aug 30, 2020), 4666 cases and 1373 deaths in in-centre haemodialysis patients were reported to the UK's Renal Registry, a case fatality rate of 29%. In the UK, although these patients were treated as clinically extremely

vulnerable, they were unable to fully shield because of mandatory life-sustaining attendance at haemodialysis (typically three 4-h sessions per week), and instances of in-unit transmission have been shown by sequencing viral isolates. For more details, read the link below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01854-7/fulltext

REPORT

Publication Date: Aug 16, 2021

Combining spike- and nucleocapsid-based vaccines improves distal control of SARS-CoV-2

SARS-CoV-2 infection causes respiratory insufficiency and neurological manifestations, including loss of smell and psychiatric disorders, and can be fatal. Most vaccines are based on the spike antigen alone, and although they have shown efficacy at preventing severe disease and death, they do not always confer sterilizing immunity. Here, it was interrogated whether SARS-CoV-2 vaccines could be improved by incorporating nucleocapsid as an antigen. We show that, after 72 h of challenge, a spike-based vaccine confers acute protection in the lung, but not in the brain. However, combining a spike-based vaccine with a nucleocapsid-based vaccine confers acute protection in both the lung and brain. These findings suggest that nucleocapsid-specific immunity can improve the distal control of SARS-CoV-2, warranting the inclusion of nucleocapsid in next-generation COVID-19 vaccines.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01108-6

Publication Date: Aug 13, 2021

Structural and functional ramifications of antigenic drift in recent SARS-CoV-2 variants

Neutralizing antibodies (nAbs) elicited against the receptor binding site (RBS) of the spike protein of wild-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are generally less effective against recent variants of concern. RBS residues Glu484, Lys417, and Asn501 are mutated in variants first described in South Africa (B.1.351) and Brazil (P.1). Their effects were analyzed on angiotensin-converting enzyme 2 binding, as well as the effects of two of these mutations (K417N and E484K) on nAbs isolated from COVID-19 patients. Binding and neutralization of the two most frequently elicited antibody families (IGHV3-53/3-66 and IGHV1-2), which can both bind the RBS in alternative binding modes, are abrogated by K417N, E484K, or both. These effects

can be structurally explained by their extensive interactions with RBS nAbs. However, nAbs to the more conserved, cross-neutralizing CR3022 and S309 sites were largely unaffected. The results have implications for next-generation vaccines and antibody therapies.

Reference

https://www.science.org/doi/10.1126/science.abh1139

Publication Date: Aug 12, 2021

Acute SARS-CoV-2 infection is associated with an increased abundance of bacterial pathogens, including *Pseudomonas aeruginosa* in the nose

Research conducted on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogenesis and coronavirus disease 2019 (COVID-19) generally focuses on the systemic host response, especially that generated by severely ill patients, with few studies investigating the impact of acute SARS-CoV-2 at the site of infection. It was shown that the nasal microbiome of SARS-CoV-2-positive patients (CoV+, n = 68) at the time of diagnosis is unique when compared to CoV− healthcare workers (n = 45) and CoV− outpatients (n = 21). This shift is marked by an increased abundance of bacterial pathogens, including Pseudomonas aeruginosa, which is also positively associated with viral RNA load. Additionally, we observe a robust host transcriptional response in the nasal epithelia of CoV+ patients, indicative of an antiviral innate immune response and neuronal damage. These data suggest that the inflammatory response caused by SARS-CoV-2 infection is associated with an increased abundance of bacterial pathogens in the nasal cavity that could contribute to increased incidence of secondary bacterial infections.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01080-9

Durability of mRNA-1273 vaccine–induced antibodies against SARS-CoV-2 variants

SARS-CoV-2 mutations may diminish vaccine-induced protective immune responses, particularly as antibody titers wane over time. Here, we assess the impact of SARS-

CoV-2 variants B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.429 (Epsilon), B.1.526 (Iota), and B.1.617.2 (Delta) on binding, neutralizing, and ACE2-competing antibodies elicited by the vaccine mRNA-1273 over seven months. Cross-reactive neutralizing responses were rare after a single dose. At the peak of response to the second vaccine dose, all individuals had responses to all variants. Binding and functional antibodies against variants persisted in most subjects, albeit at low levels, for 6-months after the primary series of the mRNA-1273 vaccine. Across all assays, B.1.351 had the lowest antibody recognition. These data complement ongoing studies to inform the potential need for additional boost vaccinations.

Reference

https://www.science.org/doi/10.1126/science.abj4176

NEWS LETTER

Publication Date: Aug 18, 2021

COVID-19 vaccines may trigger superimmunity in people who had SARS long ago

Almost 20 years before SARS-CoV-2, a related and even more lethal coronavirus sowed panic, killing nearly 10% of the 8000 people who became infected. But the 2003 outbreak of severe acute respiratory syndrome (SARS) may have left some survivors with a gift. Former SARS patients who have been vaccinated against COVID-19 appear able to fend off all variants of SARS-CoV-2 in circulation, as well as ones that may soon emerge, a new study suggests. Their formidable antibodies may even protect against coronaviruses in other species that have yet to make the jump into humans—and may hold clues to how to make a so-called pancoronavirus vaccine that could forestall future outbreaks.

A team led by emerging disease specialist Linfa Wang from Duke-NUS Medical School in Singapore identified eight SARS survivors who recently received two shots of a messenger RNA COVID-19 vaccine. In the test tube, antibodies sieved from their blood potently “neutralized” an early strain of SARS-CoV-2 as well as SARS-CoV, the virus that caused SARS, Wang and colleagues report today in The New England Journal of Medicine. The team further found these neutralizing antibodies worked well against the Alpha, Beta, and Delta variants of SARS-CoV-2 and stymied five related coronaviruses found in bats and pangolins that potentially could infect humans. For more details, read the link given below.

Reference

https://www.science.org/content/article/covid-19-vaccines-may-trigger-superimmunity-people-who-had-sars-long-ago