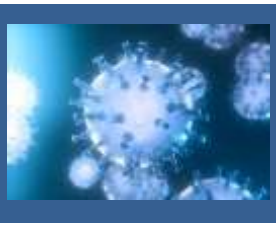
COVID-19

Oct 14 – 20, 2021



RESEARCH PUBLICATIONS

Publication Date: Oct 20, 2021

An alphavirus replicon-based vaccine expressing a stabilized Spike antigen induces protective immunity and prevents transmission of SARS-CoV-2 between cats

Abstract

Early in the SARS-CoV-2 pandemic concerns were raised regarding infection of new animal hosts and the effect on viral epidemiology. Infection of other animals could be detrimental by causing clinical disease, allowing further mutations, and bares the risk for the establishment of a non-human reservoir. Cats were the first reported animals susceptible to natural and experimental infection with SARS-CoV-2. Given the concerns these findings raised, and the close contact between humans and cats, we aimed to develop a vaccine candidate that could reduce SARS-CoV-2 infection and in addition to prevent spread among cats. Here we report that a Replicon Particle (RP) vaccine based on Venezuelan equine encephalitis virus, known to be safe and efficacious in a variety of animal species, could induce neutralizing antibody responses in guinea pigs and cats. The design of the SARS-CoV-2 spike immunogen was critical in developing a strong neutralizing antibody response. Vaccination of cats was able to induce high neutralizing antibody responses, effective also against the SARS-CoV-2 B.1.1.7 variant. Interestingly, in contrast to control animals, the infectious virus could not be detected in oropharyngeal or nasal swabs of vaccinated cats after SARS-CoV-2 challenge. Correspondingly, the challenged control cats spread the virus to in-contact cats whereas the vaccinated cats did not transmit the virus. The results show that the RP vaccine induces protective immunity preventing SARS-CoV-2 infection and transmission. These data suggest that this RP vaccine could be a multi-species vaccine

useful to prevent infection and spread to and between animals should that approach be required.

Reference

https://www.nature.com/articles/s41541-021-00390-9

Hybrid immunity improves B cells and antibodies against SARS-CoV-2 variants

Abstract

The emergence of SARS-CoV-2 variants is jeopardizing the effectiveness of current vaccines and limiting the application of monoclonal antibody-based therapy for COVID-191,2. Here we analysed at single-cell level the memory B cells of five naive and five convalescent people vaccinated with the BNT162b2 mRNA vaccine to dissect the nature of the B cell and antibody response. Almost six-thousands cells were sorted, over three-thousand of them produced monoclonal antibodies against the spike protein and more than four hundred neutralized the original Wuhan SARS-CoV-2 virus. The B.1.351 (Beta) and B.1.1.248 (Gamma) variants showed to escape almost seventy per cent of these antibodies while a much smaller portion was impacted by the B.1.1.7 (Alpha) and B.1.617.2 (Delta) variants. The overall loss of neutralization was always significantly higher in the antibodies from naive people. In part this was due to the IGHV2-5;IGHJ4-1 germline, which was found only in convalescent people and generated potent and broadly neutralizing antibodies. Our data suggest that people that are seropositive following infection or primary vaccination will produce antibodies with increased potency and breadth and will be able to better control SARS-CoV-2 emerging variants.

Reference

https://www.nature.com/articles/s41586-021-04117-7

Discovery and characterization of high-affinity, potent SARS-CoV-2 neutralizing antibodies *via* single B cell screening

Abstract

Highly efficacious Monoclonal antibodies that target SARS-CoV-2 with high affinity are valuable for a wide range of biomedical applications involving novel coronavirus disease

(COVID-19) diagnosis, treatment, and prophylactic intervention. Strategies for the rapid and reliable isolation of these antibodies, especially potent neutralizing antibodies, are critical toward improved COVID-19 response and informed future response to emergent infectious diseases. In this study, single B cell screening was used to interrogate antibody repertoires of immunized mice and isolate antigen-specific IgG1+ memory B cells. Using these methods, high-affinity, potent neutralizing antibodies were identified that target the receptor-binding domain of SARS-CoV-2. Further engineering of the identified molecules to increase valency resulted in enhanced neutralizing activity. Mechanistic investigation revealed that these antibodies compete with ACE2 for binding to the receptor-binding domain of SARS-CoV-2. These antibodies may warrant further development for urgent COVID-19 applications. Overall, these results highlight the potential of single B cell screening for the rapid and reliable identification of high-affinity, potent neutralizing antibodies for infectious disease applications.

Reference

https://www.nature.com/articles/s41598-021-99401-x

Evidence for retained spike-binding and neutralizing activity against emerging SARS-CoV-2 variants in serum of COVID-19 mRNA vaccine recipients

Abstract

Background: Highly efficacious vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed. However, the emergence of viral variants that are more infectious than the earlier SARS-CoV-2 strains is concerning. Several of these viral variants have the potential to partially escape neutralizing antibody responses, warranting continued immune-monitoring.

Methods: We used a panel of 30 post-mRNA vaccination sera to determine neutralization and RBD and spike binding activity against a number of emerging viral variants. The virus neutralization was determined using authentic SARS-CoV-2 clinical isolates in an assay format that mimics physiological conditions.

Findings: We tested seven currently circulating viral variants of concern/interest, including the three Iota sublineages, Alpha (E484K), Beta, Delta and Lambda in neutralization assays. We found only small decreases in neutralization against Iota and

Delta. The reduction was stronger against a sub-variant of Lambda, followed by Beta and Alpha (E484K). Lambda is currently circulating in parts of Latin America and was detected in Germany, the US and Israel. Of note, reduction in a receptor binding domain and spike binding assay that also included Gamma, Kappa and A.23.1 was negligible.

Interpretation: Taken together, these findings suggest that mRNA SARS-CoV-2 vaccines may remain effective against these viral variants of concern/interest and that spike binding antibody tests likely retain specificity in the face of evolving SARS-CoV-2 diversity.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00419-9/fulltext

Mechanism of a COVID-19 nanoparticle vaccine candidate that elicits a broadly neutralizing antibody response to SARS-CoV-2 variants

Abstract

Vaccines that induce potent neutralizing antibody (NAb) responses against emerging variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are essential for combating the coronavirus disease 2019 (COVID-19) pandemic. We demonstrated that mouse plasma induced by self-assembling protein nanoparticles (SApNPs) that present 20 rationally designed S2GΔHR2 spikes of the ancestral Wuhan-Hu-1 strain can neutralize the B.1.1.7, B.1.351, P.1, and B.1.617 variants with comparable potency. The adjuvant effect on vaccine-induced immunity was investigated by testing 16 formulations for the multilayered I3-01v9 SApNP. Using single-cell sorting, monoclonal antibodies (mAbs) with diverse neutralization breadth and potency were isolated from mice immunized with the receptor binding domain (RBD), S2GΔHR2 spike, and SApNP vaccines. The mechanism of vaccine-induced immunity was examined in the mouse model. Compared with the soluble spike, the I3-01v9 SApNP showed sixfold longer retention, fourfold greater presentation on follicular dendritic cell dendrites, and fivefold stronger germinal center reactions in lymph node follicles.

Reference

https://www.science.org/doi/10.1126/sciadv.abj3107

Isolation of a panel of ultra-potent human antibodies neutralizing SARS-CoV-2 and viral variants of concern

Abstract

In the absence of virus-targeting small-molecule drugs approved for the treatment and prevention of COVID-19, broadening the repertoire of potent SARS-CoV-2-neutralizing antibodies represents an important area of research in response to the ongoing pandemic. Systematic analysis of such antibodies and their combinations can be particularly instrumental for identification of candidates that may prove resistant to the emerging viral escape variants. Here, we isolated a panel of 23 RBD-specific human monoclonal antibodies from the B cells of convalescent patients. A surprisingly large proportion of such antibodies displayed potent virus-neutralizing activity both in vitro and in vivo. Four of the isolated nAbs can be categorized as ultrapotent with an apparent IC100 below 16 ng/mL. We show that individual nAbs as well as dual combinations thereof retain activity against currently circulating SARS-CoV-2 variants of concern (such as B.1.1.7, B.1.351, B.1.617, and C.37), as well as against other viral variants. When used as a prophylactics or therapeutics, these nAbs could potently suppress viral replication and prevent lung pathology in SARS-CoV-2-infected hamsters. Our data contribute to the rational development of oligoclonal therapeutic nAb cocktails mitigating the risk of SARS-CoV-2 escape.

Reference

https://www.nature.com/articles/s41421-021-00340-8

Isolation of a panel of ultra-potent human antibodies neutralizing SARS-CoV-2 and viral variants of concern

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In the absence of virus-targeting small-molecule drugs approved for the treatment and prevention of COVID-19, broadening the repertoire of potent SARS-CoV-2-neutralizing antibodies represents an important area of research in response to the ongoing pandemic. Systematic analysis of such antibodies and their combinations can be particularly instrumental for identification of candidates that may prove resistant to the

emerging viral escape variants. Here, we isolated a panel of 23 RBD-specific human monoclonal antibodies from the B cells of convalescent patients. A surprisingly large proportion of such antibodies displayed potent virus-neutralizing activity both in vitro and in vivo. Four of the isolated nAbs can be categorized as ultrapotent with an apparent IC100 below 16 ng/mL. We show that individual nAbs as well as dual combinations thereof retain activity against currently circulating SARS-CoV-2 variants of concern (such as B.1.1.7, B.1.351, B.1.617, and C.37), as well as against other viral variants. When used as a prophylactics or therapeutics, these nAbs could potently suppress viral replication and prevent lung pathology in SARS-CoV-2-infected hamsters. Our data contribute to the rational development of oligoclonal therapeutic nAb cocktails mitigating the risk of SARS-CoV-2 escape.

Reference

https://www.nature.com/articles/s41421-021-00340-8

The immunology of asymptomatic SARS-CoV-2 infection: what are the key questions?

Abstract

An important challenge during the COVID-19 pandemic has been to understand asymptomatic disease and the extent to which this may be a source of transmission. As asymptomatic disease is by definition hard to screen for, there is a lack of clarity about this aspect of the COVID-19 spectrum. Studies have considered whether the prevalence of asymptomatic disease is determined by differences in age, demographics, viral load, duration of shedding, and magnitude or durability of immunity. It is clear that adaptive immunity is strongly activated during asymptomatic infection, but some features of the T cell and antibody response may differ from those in symptomatic disease. Areas that need greater clarity include the extent to which asymptomatic disease leads to persistent symptoms (long COVID), and the quality, quantity and durability of immune priming required to confer subsequent protection.

Reference

https://www.nature.com/articles/s41577-021-00631-x

Collaboration in the time of COVID: A scientometric analysis of multidisciplinary SARS-CoV-2 research

Abstract

The novel coronavirus SARS-CoV-2 and the COVID-19 illness it causes have inspired unprecedented levels of multidisciplinary research in an effort to address a generational public health challenge. In this work we conduct a scientometric analysis of COVID-19 research, paying particular attention to the nature of collaboration that this pandemic has fostered among different disciplines. Increased multidisciplinary collaboration has been shown to produce greater scientific impact, albeit with higher co-ordination costs. As such, we consider a collection of over 166,000 COVID-19-related articles to assess the scale and diversity of collaboration in COVID-19 research, which we compare to non-COVID-19 controls before and during the pandemic. We show that COVID-19 research teams are not only significantly smaller than their non-COVID-19 counterparts, but they are also more diverse. Furthermore, we find that COVID-19 research has increased the multidisciplinarity of authors across most scientific fields of study, indicating that COVID-19 has helped to remove some of the barriers that usually exist between disparate disciplines. Finally, we highlight a number of interesting areas of multidisciplinary research during COVID-19, and propose methodologies for visualising the nature of multidisciplinary collaboration, which may have application beyond this pandemic.

Reference

https://www.nature.com/articles/s41599-021-00922-7

Identification of serum prognostic biomarkers of severe COVID-19 using a quantitative proteomic approach

Abstract

The COVID-19 pandemic is an unprecedented threat to humanity that has provoked global health concerns. Since the etiopathogenesis of this illness is not fully characterized, the prognostic factors enabling treatment decisions have not been well documented. Accurately predicting the progression of the disease would aid in appropriate patient categorization and thus help determine the best treatment option.

Here, we have introduced a proteomic approach utilizing data-independent acquisition mass spectrometry (DIA-MS) to identify the serum proteins that are closely associated with COVID-19 prognosis. Twenty-seven proteins were differentially expressed between severely ill COVID-19 patients with an adverse or favorable prognosis. Ingenuity Pathway Analysis revealed that 15 of the 27 proteins might be regulated by cytokine signaling relevant to interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF), and their differential expression was implicated in the systemic inflammatory response and in cardiovascular disorders. We further evaluated practical predictors of the clinical prognosis of severe COVID-19 patients. Subsequent ELISA assays revealed that CHI3L1 and IGFALS may serve as highly sensitive prognostic markers. Our findings can help formulate a diagnostic approach for accurately identifying COVID-19 patients with severe disease and for providing appropriate treatment based on their predicted prognosis.

Reference

https://www.nature.com/articles/s41598-021-98253-9

Maternal SARS-CoV-2 infection elicits sexually dimorphic placental immune responses

Abstract

There is a persistent bias toward higher prevalence and increased severity of coronavirus disease 2019 (COVID-19) in males. Underlying mechanisms accounting for this sex difference remain incompletely understood. Interferon responses have been implicated as a modulator of COVID-19 disease in adults and play a key role in the placental antiviral response. Moreover, the interferon response has been shown to alter Fc receptor expression and therefore may affect placental antibody transfer. Here, we examined the intersection of maternal-fetal antibody transfer, viral-induced placental interferon responses, and fetal sex in pregnant women infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Placental Fc receptor abundance, interferon-stimulated gene (ISG) expression, and SARS-CoV-2 antibody transfer were interrogated in 68 human pregnancies. Sexually dimorphic expression of placental Fc receptors, ISGs and proteins, and interleukin-10 was observed after maternal SARS-CoV-2 infection, with up-regulation of these features in placental tissue of pregnant

individuals with male fetuses. Reduced maternal SARS-CoV-2–specific antibody titers and impaired placental antibody transfer were also observed in pregnancies with a male fetus. These results demonstrate fetal sex-specific maternal and placental adaptive and innate immune responses to SARS-CoV-2.

Reference

https://www.science.org/doi/10.1126/scitranslmed.abi7428

COVID-19 mRNA vaccines drive differential antibody Fc-functional profiles in pregnant, lactating, and nonpregnant women

Abstract

Substantial immunological changes occur throughout pregnancy to render the mother immunologically tolerant to the fetus and allow fetal growth. However, additional local and systemic immunological adaptations also occur, allowing the maternal immune system to continue to protect the dyad against pathogens both during pregnancy and after birth through lactation. This fine balance of tolerance and immunity, along with physiological and hormonal changes, contributes to increased susceptibility to particular infections in pregnancy, including more severe coronavirus disease 2019 (COVID-19). Whether these changes also make pregnant women less responsive to vaccination or induce altered immune responses to vaccination remains incompletely understood. To define potential changes in vaccine response during pregnancy and lactation, we undertook deep sequencing of the humoral vaccine response in a group of pregnant and lactating women and nonpregnant age-matched controls. Vaccine-specific titers were comparable between pregnant women, lactating women, and nonpregnant controls. However, Fc receptor (FcR) binding and antibody effector functions were induced with delayed kinetics in both pregnant and lactating women compared with nonpregnant women after the first vaccine dose, which normalized after the second dose. Vaccine boosting resulted in high FcR-binding titers in breastmilk. These data suggest that pregnancy promotes resistance to generating proinflammatory antibodies and indicates that there is a critical need to follow prime-boost timelines in this vulnerable population to ensure full immunity is attained.

Reference

https://www.science.org/doi/10.1126/scitranslmed.abi8631

Publication Date: Oct 18, 2021

Visible blue light inhibits infection and replication of SARS-CoV-2 at doses that are well-tolerated by human respiratory tissue

Abstract

The delivery of safe, visible wavelengths of light can be an effective, pathogen-agnostic, countermeasure that would expand the current portfolio of SARS-CoV-2 intervention strategies beyond the conventional approaches of vaccine, antibody, and antiviral therapeutics. Employing custom biological light units, that incorporate optically engineered light-emitting diode (LED) arrays, we harnessed monochromatic wavelengths of light for uniform delivery across biological surfaces. We demonstrated that primary 3D human tracheal/bronchial-derived epithelial tissues tolerated high doses of a narrow spectral band of visible light centered at a peak wavelength of 425 nm. We extended these studies to Vero E6 cells to understand how light may influence the viability of a mammalian cell line conventionally used for assaying SARS-CoV-2. The exposure of single-cell monolayers of Vero E6 cells to similar doses of 425 nm blue light resulted in viabilities that were dependent on dose and cell density. Doses of 425 nm blue light that are well-tolerated by Vero E6 cells also inhibited infection and replication of cell-associated SARS-CoV-2 by > 99% 24 h post-infection after a single five-minute light exposure. Moreover, the 425 nm blue light inactivated cell-free betacoronaviruses including SARS-CoV-1, MERS-CoV, and SARS-CoV-2 up to 99.99% in a dose-dependent manner. Importantly, clinically applicable doses of 425 nm blue light dramatically inhibited SARS-CoV-2 infection and replication in primary human 3D tracheal/bronchial tissue. Safe doses of visible light should be considered part of the strategic portfolio for the development of SARS-CoV-2 therapeutic countermeasures to mitigate coronavirus disease 2019 (COVID-19).

Reference

https://www.nature.com/articles/s41598-021-99917-2

Preclinical characterization of an intravenous coronavirus 3CL protease inhibitor for the potential treatment of COVID19

Abstract

COVID-19 caused by the SARS-CoV-2 virus has become a global pandemic. 3CL protease is a virally encoded protein that is essential across a broad spectrum of coronaviruses with no close human analogs. PF-00835231, a 3CL protease inhibitor, has exhibited potent in vitro antiviral activity against SARS-CoV-2 as a single agent. Here we report, the design and characterization of a phosphate prodrug PF-07304814 to enable the delivery and projected sustained systemic exposure in human of PF-00835231 to inhibit coronavirus family 3CL protease activity with selectivity over human host protease targets. Furthermore, we show that PF-00835231 has additive/synergistic activity in combination with remdesivir. We present the ADME, safety, in vitro, and in vivo antiviral activity data that supports the clinical evaluation of PF-07304814 as a potential COVID-19 treatment.

Reference

https://www.nature.com/articles/s41467-021-26239-2

Publication Date: Oct 17, 2021

Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic Covid-19 infection in Sweden: A nationwide cohort study

Abstract

Background: The effectiveness of heterologous prime-boost Coronavirus disease 2019 (Covid-19) vaccination is currently unknown.

Methods: From individuals vaccinated with two doses against Covid-19 in Sweden until July 5, 2021 (N=3,445,061), we formed a study cohort including 94,569 individuals that had received heterologous ChAdOx1 nCoV-19 / BNT162b2 prime-boost vaccination, 16,402 individuals that received heterologous ChAdOx1 nCoV-19 / mRNA-1273 prime-boost vaccination, and 430,100 individuals that received homologous ChAdOx1 nCoV-19 / ChAdOx1 nCoV-19 prime-boost vaccination. In addition, 180,716 individuals were

selected who were unvaccinated at the date of vaccination in the corresponding case. Unvaccinated individuals were censored at first dose of any vaccine. Baseline was the date of the second dose of any vaccine, with the same date in the corresponding unvaccinated individual. The outcome included incident symptomatic Covid-19 infection occurring >14 days after baseline.

Findings: During a mean follow-up time of 76 (range 1-183) days, symptomatic Covid-19 infection was confirmed in 187 individuals with heterologous vaccine schedules (incidence rate: 2.0/100,000 person-days) and in 306 individuals from the unvaccinated control group (incidence rate: 7.1/100,000 person-days). The adjusted vaccine effectiveness was 67% (95% CI, 59-73, P<0.001) for heterologous ChAdOx1 nCoV-19 / BNT162b2 prime-boost vaccination, and 79% (95% CI, 62-88, P<0.001) for heterologous ChAdOx1 nCoV-19 / mRNA-1273 prime-boost vaccination. When combined and analysed together, the two heterologous vaccine schedules had an effectiveness of 68% (95% CI, 61-74, P<0.001) which was significantly greater (Pinteraction<0.001) than the 50% effectiveness for homologous ChAdOx1 nCoV-19 / ChAdOx1 nCoV-19 (95% CI, 41-58, P<0.001).

Interpretation: The findings of this study suggest that the use of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination is an effective alternative to increase population immunity against Covid-19, including against the Delta variant which dominated the confirmed cases during the study period. These findings could have important implications for vaccination strategies and logistics, and consequently in the battle against the Covid-19 pandemic.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00235-0/fulltext

BNT162b2 mRNA COVID-19 vaccination in immunocompromised patients: A prospective cohort study

Abstract

Background: Trials of the Pfizer-BioNTech BNT162b2 mRNA vaccine showed 95% efficacy in preventing symptomatic disease; however, the trials excluded immunocompromised patients (ICPs). We aim at analyzing antibody response in ICPs.

Methods: A prospective cohort study was conducted at Sheba Medical Center, Israel, between January and April 2020, in 1274 participants who received the vaccine, including 1002 ICPs and 272 immunocompetent healthcare workers (HCWs). Antibodies were measured two-four weeks after vaccination by SARS-CoV-2 anti–receptor binding domain IgG antibodies (RBD IgG) and pseudo-virus neutralization assays. Multivariable logistic regression analyses were used to identify factors associated with vaccine-induced antibody response. Adverse events (AEs) were monitored.

Findings: RBD-IgG antibodies were detected in 154/156 (98.7%) of patients with HIV, 75/90 (83.3%) with solid malignancies, 149/187 (79.7%) with myeloma, 83/111 (74.8%) following hematopoietic stem cell transplants, 25/36 (69.4%) following liver transplantation, 26/43 (60.5%) with myelodysplastic syndrome, 96/188 (51.0%) with chronic lymphocytic leukemia/non-Hodgkin's lymphoma, 50/110 (45.5%) following kidney transplantation, 15/80 (18.8%) following heart transplantation, and 269/272 (98.9%) in controls. There was a significant correlation r = 0.74 (95%CI 0.69,0.78) between RBD-binding IgG and neutralizing antibodies in all groups. Multivariate logistic regression analysis showed that age > 65 years (OR 0.41,95%CI 0.30,0.57) and underlying immunosuppression (OR 0.02,95%CI 0.01,0.07) were significantly associated with a non-reactive response of IgG antibodies. HIV patients showed a similar immunological response as healthy adults. The vaccine was safe without any episodes of rejection, graft-versus-host disease (GVHD) or allergy. Immunocompetent HCWs experienced significantly more AEs than ICPs.

Interpretation: Antibody response to the Pfizer-BioNTech vaccine was highly variable among different ICPs; thus, individual recommendations should be provided for the different immunosuppression states.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00438-7/fulltext

The effectiveness of various gargle formulations and salt water against SARS-CoV-2

Abstract

The COVID-19 is difficult to contain due to its high transmissibility rate and a long incubation period of 5 to 14 days. Moreover, more than half of the infected patients were young and asymptomatic. Virus transmission through asymptomatic patients is a major challenge to disease containment. Due to limited treatment options, preventive measures play major role in controlling the disease spread. Gargling with antiseptic formulation may have potential role in eliminating the virus in the throat. Four commercially available mouthwash/gargle formulations were tested for virucidal activity against SARS-CoV-2 in both clean (0.3 g/l BSA) and dirty (0.3 g/l BSA + 3 mL/L human erythrocytes) conditions at time points 30 and 60 s. The virus was isolated and propagated in Vero E6 cells. The cytotoxicity of the products to the Vero E6 was evaluated by kill time assay based on the European Standard EN14476:2013/FprA1:2015 protocol. Virus titres were calculated as 50% tissue culture infectious dose (TCID50/mL) using the Spearman-Karber method. A reduction in virus titer of 4 log10 corresponds to an inactivation of ≥ 99.99%. Formulations with cetylperidinium chloride, chlorhexidine and hexitidine achieved > 4 log10 reduction in viral titres when exposed within 30 s under both clean and dirty conditions. Thymol formulations achieved only 0.5 log10 reduction in viral titres. In addition, salt water was not proven effective. Gargle formulations with cetylperidinium chloride, chlorhexidine and hexetidine have great potential in reducing SAR-CoV-2 at the source of entry into the body, thus minimizing risk of transmission of COVID-19.

Reference

https://www.nature.com/articles/s41598-021-99866-w

Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy

Abstract

Background: Sphingosine-1-phosphate receptor (S1P) modulators and anti-CD20 therapies impair humoral responses to SARS-CoV-2 mRNA vaccines. Relatively few studies have assessed the impact of an array of disease modifying therapies (DMTs) for multiple sclerosis (MS) on T cell immune responses to SARS-CoV-2 vaccination.

Methods: In 101 people with MS, we measured humoral responses via an immunoassay to measure IgG against the COVID-19 spike S1 glycoprotein in serum. We also measured T cell responses using FluoroSpot assay for interferon gamma (IFN-γ) (Mabtech, Sweden) using cryopreserved rested PBMCs and then incubated in cRPMI with 1µg/ml of pooled peptides spanning the entire spike glycoprotein (Genscript, 2 pools; 158 peptides each). Plates were read on an AID iSpot Spectrum to determine the number of spot forming cells (SFC)/106 PBMCs. We tested for differences in immune responses across DMTs using linear models.

Findings: Humoral responses were detected in 22/39 (56.4%) participants on anti-CD20 and in 59/63 (93.6%) participants on no or other DMTs. In a subset (n=88; 87%), T cell responses were detected in 76/88 (86%), including 32/33 (96.9%) participants on anti-CD20 therapies. Anti-CD20 therapies were associated with an increase in IFN-γ SFC counts relative to those on no DMT or other DMTs (for anti-CD20 vs. no DMT: 425.9% higher [95%CI: 109.6%, 1206.6%] higher; $p<0.001$; for anti-CD20 vs. other DMTs: 289.6% [95%CI: 85.9%, 716.6%] higher; $p<0.001$).

Interpretation: We identified a robust T cell response in individuals on anti-CD20 therapies despite a reduced humoral response to SARS-CoV-2 vaccination. Follow up studies are needed to determine if this translates to protection against COVID-19 infection.

Funding: This study was funded partially by 1K01MH121582-01 from NIH/NIMH and TA-1805-31136 from the National MS Society (NMSS) to KCF and TA-1503-03465 and JF-2007-37655 from the NMSS to PB. This study was also supported through the generosity of the collective community of donors to the Johns Hopkins University School of Medicine for COVID research.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00429-1/fulltext

Publication Date: Oct 14, 2021

Integrin activation is an essential component of SARS-CoV-2 infection

Abstract

SARS-CoV-2 infection depends on binding its spike (S) protein to angiotensin-converting enzyme 2 (ACE2). The S protein expresses an RGD motif, suggesting that integrins may be co-receptors. Here, we UV-inactivated SARS-CoV-2 and fluorescently labeled the envelope membrane with octadecyl rhodamine B (R18) to explore the role of integrin activation in mediating cell entry and productive infection. We used flow cytometry and confocal microscopy to show that SARS-CoV-2R18 particles engage basal-state integrins. Furthermore, we demonstrate that Mn2+, which induces integrin extension, enhances cell entry of SARS-CoV-2R18. We also show that one class of integrin antagonist, which binds to the αI MIDAS site and stabilizes the inactive, closed conformation, selectively inhibits the engagement of SARS-CoV-2R18 with basal state integrins, but is ineffective against Mn2+-activated integrins. RGD-integrin antagonists inhibited SARS-CoV-2R18 binding regardless of integrin activation status. Integrins transmit signals bidirectionally: 'inside-out' signaling primes the ligand-binding function of integrins via a talin-dependent mechanism, and 'outside-in' signaling occurs downstream of integrin binding to macromolecular ligands. Outside-in signaling is mediated by Gα13. Using cell-permeable peptide inhibitors of talin and Gα13 binding to the cytoplasmic tail of an integrin's β subunit, we demonstrate that talin-mediated signaling is essential for productive infection.

Reference

https://www.nature.com/articles/s41598-021-99893-7

Fluorescent glycan fingerprinting of SARS2 spike proteins

Abstract

Glycosylation is the most common post-translational modification and has myriad of biological functions. However, glycan analysis has always been a challenge. Here, we

would like to present new techniques for glycan fingerprinting based on enzymatic fluorescent labeling and gel electrophoresis. The method is illustrated on SARS2 spike (S) glycoproteins. SARS2, a novel coronavirus and the causative agent of the COVID-19 pandemic, has had significant social and economic impacts since the end of 2019. To obtain the N-glycan fingerprint of an S protein, glycans released from the protein are first labeled through enzymatic incorporation of fluorophore-conjugated sialic acid or fucose, then separated by SDS-PAGE, and finally visualized with a fluorescent imager. To identify the labeled glycans of a fingerprint, glycan standards and glycan ladders are enzymatically generated and run alongside the samples as references. By comparing the mobility of a labeled glycan to that of a glycan standard, the identity of glycans maybe determined. O-glycans can also be fingerprinted. Due to the lack of an enzyme for broad O-glycan release, O-glycans on the S protein can be labeled with fluorescent sialic acid and digested with trypsin to obtain labeled glycan peptides that are then separated by gel electrophoresis. Glycan fingerprinting could serve as a quick method for globally assessing the glycosylation of a specific glycoprotein.

Reference

https://www.nature.com/articles/s41598-021-98919-4

INO-4800 DNA vaccine induces neutralizing antibodies and T cell activity against global SARS-CoV-2 variants

Abstract

Global surveillance has identified emerging SARS-CoV-2 variants of concern (VOC) associated with broadened host specificity, pathogenicity, and immune evasion to vaccine-induced immunity. Here we compared humoral and cellular responses against SARS-CoV-2 VOC in subjects immunized with the DNA vaccine, INO-4800. INO-4800 vaccination induced neutralizing antibodies against all variants tested, with reduced levels detected against B.1.351. IFNγ T cell responses were fully maintained against all variants tested.

Reference

https://www.nature.com/articles/s41541-021-00384-7

Rapid incidence estimation from SARS-CoV-2 genomes reveals decreased case detection in Europe during summer 2020

Abstract

By October 2021, 230 million SARS-CoV-2 diagnoses have been reported. Yet, a considerable proportion of cases remains undetected. Here, we propose GInPipe, a method that rapidly reconstructs SARS-CoV-2 incidence profiles solely from publicly available, time-stamped viral genomes. We validate GInPipe against simulated outbreaks and elaborate phylodynamic analyses. Using available sequence data, we reconstruct incidence histories for Denmark, Scotland, Switzerland, and Victoria (Australia) and demonstrate, how to use the method to investigate the effects of changing testing policies on case ascertainment. Specifically, we find that under-reporting was highest during summer 2020 in Europe, coinciding with more liberal testing policies at times of low testing capacities. Due to the increased use of real-time sequencing, it is envisaged that GInPipe can complement established surveillance tools to monitor the SARS-CoV-2 pandemic. In post-pandemic times, when diagnostic efforts are decreasing, GInPipe may facilitate the detection of hidden infection dynamics.

Reference

https://www.nature.com/articles/s41467-021-26267-y

Surveillance of SARS-CoV-2 lineage B.1.1.7 in Slovakia using a novel, multiplexed RT-qPCR assay

Abstract

The emergence of a novel SARS-CoV-2 B.1.1.7 variant sparked global alarm due to increased transmissibility, mortality, and uncertainty about vaccine efficacy, thus accelerating efforts to detect and track the variant. Current approaches to detect B.1.1.7 include sequencing and RT-qPCR tests containing a target assay that fails or results in reduced sensitivity towards the B.1.1.7 variant. Since many countries lack genomic surveillance programs and failed assays detect unrelated variants containing similar mutations as B.1.1.7, we used allele-specific PCR, and judicious placement of LNA-modified nucleotides to develop an RT-qPCR test that accurately and rapidly differentiates B.1.1.7 from other SARS-CoV-2 variants. We validated the test on 106

clinical samples with lineage status confirmed by sequencing and conducted a country-wide surveillance study of B.1.1.7 prevalence in Slovakia. Our multiplexed RT-qPCR test showed 97% clinical sensitivity and retesting 6,886 SARS-CoV-2 positive samples obtained during three campaigns performed within one month, revealed pervasive spread of B.1.1.7 with an average prevalence of 82%. Labs can easily implement this test to rapidly scale B.1.1.7 surveillance efforts and it is particularly useful in countries with high prevalence of variants possessing only the ΔH69/ΔV70 deletion because current strategies using target failure assays incorrectly identify these as putative B.1.1.7 variants.

Reference

https://www.nature.com/articles/s41598-021-99661-7

Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK

Abstract

The effectiveness of the BNT162b2 and ChAdOx1 vaccines against new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections requires continuous re-evaluation, given the increasingly dominant B.1.617.2 (Delta) variant. In this study, we investigated the effectiveness of these vaccines in a large, community-based survey of randomly selected households across the United Kingdom. We found that the effectiveness of BNT162b2 and ChAdOx1 against infections (new polymerase chain reaction (PCR)-positive cases) with symptoms or high viral burden is reduced with the B.1.617.2 variant (absolute difference of 10–13% for BNT162b2 and 16% for ChAdOx1) compared to the B.1.1.7 (Alpha) variant. The effectiveness of two doses remains at least as great as protection afforded by prior natural infection. The dynamics of immunity after second doses differed significantly between BNT162b2 and ChAdOx1, with greater initial effectiveness against new PCR-positive cases but faster declines in protection against high viral burden and symptomatic infection with BNT162b2. There was no evidence that effectiveness varied by dosing interval, but protection was higher in vaccinated individuals after a prior infection and in younger adults. With B.1.617.2, infections occurring after two vaccinations had similar peak viral burden as those in

unvaccinated individuals. SARS-CoV-2 vaccination still reduces new infections, but effectiveness and attenuation of peak viral burden are reduced with B.1.617.2.

Reference

https://www.nature.com/articles/s41591-021-01548-7

Brain MRI in SARS-CoV-2 pneumonia patients with newly developed neurological manifestations suggestive of brain involvement

Abstract

The increased frequency of neurological manifestations, including central nervous system (CNS) manifestations, in patients with coronavirus disease 2019 (COVID-19) pandemic is consistent with the virus's neurotropic nature. In most patients, brain magnetic resonance imaging (MRI) is a sensitive imaging modality in the diagnosis of viral encephalitides in the brain. The purpose of this study was to determine the frequency of brain lesion patterns on brain MRI in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia patients who developed focal and non-focal neurological manifestations. In addition, it will compare the impact of the Glasgow Coma Scale (GCS) as an index of deteriorating cerebral function on positive brain MRIs in both neurological manifestations. This retrospective study included an examination of SARS-CoV-2 pneumonia patients with real-time reverse transcription polymerase chain reaction (RT-PCR) confirmation, admitted with clinicoradiologic evidence of COVID-19 pneumonia, and who were candidates for brain MRI due to neurological manifestations suggesting brain involvement. Brain imaging acquired on a 3.0 T MRI system (Skyra; Siemens, Erlangen, Germany) with a 20-channel receive head coil. Brain MRI revealed lesions in 38 (82.6%) of the total 46 patients for analysis and was negative in the remaining eight (17.4%) of all finally enclosed patients with RT-PCR confirmed SARS-CoV-2 pneumonia. Twenty-nine (63%) patients had focal neurological manifestations, while the remaining 17 (37%) patients had non-focal neurological manifestations. The patients had a highly significant difference ($p = 0.0006$) in GCS, but no significant difference ($p = 0.4$) in the number of comorbidities they had. Brain MRI is a feasible and important imaging modality in patients with SARS-CoV-2 pneumonia who develop neurological manifestations suggestive of brain involvement, particularly in patients with non-focal manifestations and a decline in GCS.

Reference

https://www.nature.com/articles/s41598-021-00064-5

Replication and single-cycle delivery of SARS-CoV-2 replicons

Abstract

Molecular virology tools are critical for basic studies of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and for developing new therapeutics. There remains a need for experimental systems that do not rely on viruses capable of spread that could potentially be used in lower containment settings. Here, we develop spike-deleted SARS-CoV-2 self-replicating RNAs using a yeast-based reverse genetics system. These non-infectious self-replicating RNAs, or replicons, can be trans-complemented with viral glycoproteins to generate Replicon Delivery Particles (RDPs) for single-cycle delivery into a range of cell types. This SARS-CoV-2 replicon system represents a convenient and versatile platform for antiviral drug screening, neutralization assays, host factor validation, and characterizing viral variants.

Reference

https://www.science.org/doi/10.1126/science.abj8430