COVID-19

Aug 13-19, 2020

RESEARCH PUBLICATIONS

Publication Date: Aug 19, 2020

Automated and partly automated contact tracing: a systematic review to inform the control of COVID-19

Abstract

Evidence for the use of automated or partly automated contact-tracing tools to contain severe acute respiratory syndrome coronavirus 2 is scarce. We did a systematic review of automated or partly automated contact tracing. We searched PubMed, EMBASE, OVID Global Health, EBSCO Medical COVID Information Portal, Cochrane Library, medRxiv, bioRxiv, arXiv, and Google Advanced for articles relevant to COVID-19, severe acute respiratory syndrome, Middle East respiratory syndrome, influenza, or Ebola virus, published from Jan 1, 2000, to April 14, 2020. We also included studies identified through professional networks up to April 30, 2020. We reviewed all full-text manuscripts. Primary outcomes were the number or proportion of contacts (or subsequent cases) identified. Secondary outcomes were indicators of outbreak control, uptake, resource use, cost-effectiveness, and lessons learnt. This study is registered with PROSPERO (CRD42020179822). Of the 4036 studies identified, 110 full-text studies were reviewed and 15 studies were included in the final analysis and quality assessment. No empirical evidence of the effectiveness of automated contact tracing (regarding contacts identified or transmission reduction) was identified. Four of seven included modelling studies that suggested that controlling COVID-19 requires a high population uptake of automated contact-tracing apps (estimates from 56% to 95%), typically alongside other control measures. Studies of partly automated contact tracing generally reported more complete contact identification and follow-up compared with manual systems. Automated contact tracing could potentially reduce transmission with

sufficient population uptake. However, concerns regarding privacy and equity should be considered. Well designed prospective studies are needed given gaps in evidence of effectiveness, and to investigate the integration and relative effects of manual and automated systems. Large-scale manual contact tracing is therefore still key in most contexts.

Reference

https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30184-9/fulltext

SARS-CoV-2-specific T cells exhibit phenotypic features of robust helper function, lack of terminal differentiation, and high proliferative potential

Abstract

Convalescing COVID-19 patients mount robust T cell responses against SARS-CoV-2, suggesting an important role for T cells in viral clearance. To date, the phenotypes of SARS-CoV-2-specific T cells remain poorly defined. Using 38-parameter CyTOF, we phenotyped longitudinal specimens of SARS-CoV-2-specific CD4+ and CD8+ T cells from nine individuals who recovered from mild COVID-19. SARS-CoV-2-specific CD4+ T cells were exclusively Th1 cells, and predominantly Tcm with phenotypic features of robust helper function. SARS-CoV-2-specific CD8+ T cells were predominantly Temra cells in a state of less terminal differentiation than most Temra cells. Subsets of SARS-CoV-2-specific T cells express CD127, can homeostatically proliferate, and can persist for over two months. Our results suggest that long-lived and robust T cell immunity is generated following natural SARS-CoV-2 infection, and support an important role for SARS-CoV-2-specific T cells in host control of COVID-19.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30102-6

Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: A prospective observational study'

Abstract

Overwhelming inflammatory reactions contribute to respiratory distress in patients with COVID-19. Ruxolitinib is a JAK1/JAK2 inhibitor with potent anti-inflammatory properties. We report on a prospective, observational study in 34 patients with COVID-19 who received ruxolitinib on a compassionate-use protocol. Patients had severe pulmonary disease defined by pulmonary infiltrates on imaging and an oxygen saturation ≤ 93% in air and/or PaO2/FiO2 ratio ≤ 300 mmHg. Median age was 80.5 years, and 85.3% had ≥ 2 comorbidities. Median exposure time to ruxolitinib was 13 days, median dose intensity was 20 mg/day. Overall survival by day 28 was 94.1%. Cumulative incidence of clinical improvement of ≥2 points in the ordinal scale was 82.4% (95% confidence interval, 71–93). Clinical improvement was not affected by low-flow versus high-flow oxygen support but was less frequent in patients with $PaO_2/FiO_2 < 200$ mmHg. The most frequent adverse events were anemia, urinary tract infections, and thrombocytopenia. Improvement of inflammatory cytokine profile and activated lymphocyte subsets was observed at day 14. In this prospective cohort of aged and high-risk comorbidity patients with severe COVID-19, compassionate-use ruxolitinib was safe and was associated with improvement of pulmonary function and discharge home in 85.3%. Controlled clinical trials are necessary to establish efficacy of ruxolitinib in COVID-19.

Reference

https://www.nature.com/articles/s41375-020-01018-y

Publication Date: Aug 18, 2020

Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with a 382-nucleotide deletion (Δ382) in the open reading frame 8 (ORF8) region of the genome have been detected in Singapore and other countries. We investigated the effect of this deletion on the clinical features of infection.

Methods: We retrospectively identified patients who had been screened for the Δ382 variant and recruited to the PROTECT study—a prospective observational cohort study

conducted at seven public hospitals in Singapore. We collected clinical, laboratory, and radiological data from patients' electronic medical records and serial blood and respiratory samples taken during hospitalisation and after discharge. Individuals infected with the Δ382 variant were compared with those infected with wild-type SARS-CoV-2. Exact logistic regression was used to examine the association between the infection groups and the development of hypoxia requiring supplemental oxygen (an indicator of severe COVID-19, the primary endpoint). Follow-up for the study's primary endpoint is completed.

Findings: Between Jan 22 and March 21, 2020, 278 patients with PCR-confirmed SARS-CoV-2 infection were screened for the Δ382 deletion and 131 were enrolled onto the study, of whom 92 (70%) were infected with the wild-type virus, ten (8%) had a mix of wild-type and Δ382-variant viruses, and 29 (22%) had only the Δ382 variant. Development of hypoxia requiring supplemental oxygen was less frequent in the Δ382 variant group (0 [0%] of 29 patients) than in the wild-type only group (26 [28%] of 92; absolute difference 28% [95% CI 14–28]). After adjusting for age and presence of comorbidities, infection with the Δ382 variant only was associated with lower odds of developing hypoxia requiring supplemental oxygen (adjusted odds ratio 0·07 [95% CI 0·00–0·48]) compared with infection with wild-type virus only.

Interpretation: The Δ382 variant of SARS-CoV-2 seems to be associated with a milder infection. The observed clinical effects of deletions in ORF8 could have implications for the development of treatments and vaccines.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31757-8/fulltext

Comparison of molecular testing strategies for COVID-19 control: A mathematical modelling study

Abstract

Background: WHO has called for increased testing in response to the COVID-19 pandemic, but countries have taken different approaches and the effectiveness of alternative strategies is unknown. We aimed to investigate the potential impact of

different testing and isolation strategies on transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods: We developed a mathematical model of SARS-CoV-2 transmission based on infectiousness and PCR test sensitivity over time since infection. We estimated the reduction in the effective reproduction number (R) achieved by testing and isolating symptomatic individuals, regular screening of high-risk groups irrespective of symptoms, and quarantine of contacts of laboratory-confirmed cases identified through test-and-trace protocols. The expected effectiveness of different testing strategies was defined as the percentage reduction in R. We reviewed data on the performance of antibody tests reported by the Foundation for Innovative New Diagnostics and examined their implications for the use of so-called immunity passports.

Findings: If all individuals with symptoms compatible with COVID-19 self-isolated and self-isolation was 100% effective in reducing onwards transmission, self-isolation of symptomatic individuals would result in a reduction in R of 47% (95% uncertainty interval [UI] 32–55). PCR testing to identify SARS-CoV-2 infection soon after symptom onset could reduce the number of individuals needing to self-isolate, but would also reduce the effectiveness of self-isolation (around 10% would be false negatives). Weekly screening of health-care workers and other high-risk groups irrespective of symptoms by use of PCR testing is estimated to reduce their contribution to SARS-CoV-2 transmission by 23% (95% UI 16–40), on top of reductions achieved by self-isolation following symptoms, assuming results are available at 24 h. The effectiveness of test and trace depends strongly on coverage and the timeliness of contact tracing, potentially reducing R by 26% (95% UI 14–35) on top of reductions achieved by self-isolation following symptoms, if 80% of cases and contacts are identified and there is immediate testing following symptom onset and quarantine of contacts within 24 h. Among currently available antibody tests, performance has been highly variable, with specificity around 90% or lower for rapid diagnostic tests and 95–99% for laboratory-based ELISA and chemiluminescent assays.

Interpretation: Molecular testing can play an important role in prevention of SARS-CoV-2 transmission, especially among health-care workers and other high-risk groups, but no single strategy will reduce R below 1 at current levels of population immunity.

Immunity passports based on antibody tests or tests for infection face substantial technical, legal, and ethical challenges.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30630-7/fulltext

Pharmacogenomics of COVID-19 therapies

Abstract

A new global pandemic of coronavirus disease 2019 (COVID-19) has resulted in high mortality and morbidity. Currently numerous drugs are under expedited investigations without well-established safety or efficacy data. Pharmacogenomics may allow individualization of these drugs thereby improving efficacy and safety. In this review, we summarized the pharmacogenomic literature available for COVID-19 drug therapies including hydroxychloroquine, chloroquine, azithromycin, remdesivir, favipiravir, ribavirin, lopinavir/ritonavir, darunavir/cobicistat, interferon beta-1b, tocilizumab, ruxolitinib, baricitinib, and corticosteroids. We searched PubMed, reviewed the Pharmacogenomics Knowledgebase (PharmGKB®) website, Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, the U.S. Food and Drug Administration (FDA) pharmacogenomics information in the product labeling, and the FDA pharmacogenomics association table. We found several drug-gene variant pairs that may alter the pharmacokinetics of hydroxychloroquine/chloroquine (CYP2C8, CYP2D6, SLCO1A2, and SLCO1B1); azithromycin (ABCB1); ribavirin (SLC29A1, SLC28A2, and SLC28A3); and lopinavir/ritonavir (SLCO1B1, ABCC2, CYP3A). We also identified other variants, that are associated with adverse effects, most notable in hydroxychloroquine/chloroquine (G6PD; hemolysis), ribavirin (ITPA; hemolysis), and interferon β -1b (IRF6; liver toxicity). We also describe the complexity of the risk for QT prolongation in this setting because of additive effects of combining more than one QT-prolonging drug (i.e., hydroxychloroquine/chloroquine and azithromycin), increased concentrations of the drugs due to genetic variants, along with the risk of also combining therapy with potent inhibitors. In conclusion, although direct evidence in COVID-19 patients is lacking, we identified potential actionable genetic markers in

COVID-19 therapies. Clinical studies in COVID-19 patients are deemed warranted to assess potential roles of these markers.

Reference

https://www.nature.com/articles/s41525-020-00143-y

In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges

Abstract

The spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is required for cell entry and is the major focus for vaccine development. Here, we combine cryo electron tomography, subtomogram averaging and molecular dynamics simulations to structurally analyze S in situ. Compared to recombinant S, the viral S was more heavily glycosylated and occurred mostly in the closed pre-fusion conformation. We show that the stalk domain of S contains three hinges, giving the head unexpected orientational freedom. We propose that the hinges allow S to scan the host cell surface, shielded from antibodies by an extensive glycan coat. The structure of native S contributes to our understanding of SARS-CoV-2 infection and the development of safe vaccines.

Reference

https://science.sciencemag.org/content/early/2020/08/17/science.abd5223

Spatio-temporal analysis of meteorological factors in abating the spread of COVID-19 in Africa

Abstract

In Asia, Europe and South America, the role of atmospheric condition in aiding or abating the growth curve of COVID-19 has been analysed. Howesver, no study to date has examined such climatic extensions for the growth or otherwise of the novel coronavirus in Africa. Africa, with a mostly relatively warmer temperature differs from other regions of the world and in addition, has recorded far fewer cases compared to

Asian, Europeans and the Americans (North and South). It then becomes imperative to examine the influence of meteorological indices in the growth or otherwise of coronavirus diseases in Africa to establish whether findings on the climatic conditions-COVID-19 growth are regionally specific. In this study, we examined the influence of meteorological factors for aiding or abating the spread of the aerosolised pathogen of COVID-19 in Africa. We rely on the generalised additive model (GAM) and found wind speed to positively relate to COVID-19 growth while mean temperature and relative humidity to inversely relates to COVID-19 growth curve in Africa. We accounted for potential cofounders in the core GAM model and discuss policy implications.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)31592-9

Publication Date: Aug 17, 2020

ORF8 and ORF3b antibodies are accurate serological markers of early and late SARS-CoV-2 infection

Abstract

The SARS-CoV-2 virus emerged in December 2019 and has caused a worldwide pandemic due to the lack of any pre-existing immunity. Accurate serology testing is urgently needed to help diagnose infection, determine past exposure of populations and assess the response to a future vaccine. The landscape of antibody responses to SARS-CoV-2 is unknown. In this study, we utilized the luciferase immunoprecipitation system to assess the antibody responses to 15 different SARS-CoV-2 antigens in patients with COVID-19. We identified new targets of the immune response to SARS-CoV-2 and show that nucleocapsid, open reading frame (ORF)8 and ORF3b elicit the strongest specific antibody responses. ORF8 and ORF3b antibodies, taken together as a cluster of points, identified 96.5% of COVID-19 samples at early and late time points of disease with 99.5% specificity. Our findings could be used to develop second-generation diagnostic tests to improve serological assays for COVID-19 and are important in understanding pathogenicity.

Reference

https://www.nature.com/articles/s41590-020-0773-7

COVID-19 and multisystem inflammatory syndrome in children and adolescents

Abstract

As severe acute respiratory syndrome coronavirus 2 continues to spread worldwide, there have been increasing reports from Europe, North America, Asia, and Latin America describing children and adolescents with COVID-19-associated multisystem inflammatory conditions. However, the association between multisystem inflammatory syndrome in children and COVID-19 is still unknown. We review the epidemiology, causes, clinical features, and current treatment protocols for multisystem inflammatory syndrome in children and adolescents associated with COVID-19. We also discuss the possible underlying pathophysiological mechanisms for COVID-19-induced inflammatory processes, which can lead to organ damage in paediatric patients who are severely ill. These insights provide evidence for the need to develop a clear case definition and treatment protocol for this new condition and also shed light on future therapeutic interventions and the potential for vaccine development.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30651-4/fulltext

Publication Date: Aug 14, 2020

Adaptive immune responses to SARS-CoV-2 infection in severe versus mild individuals

Abstract

The global Coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has affected more than eight million people. There is an urgent need to investigate how the adaptive immunity is established in COVID-19 patients. In this study, we profiled adaptive immune cells of PBMCs from recovered COVID-19 patients with varying disease severity using single-cell RNA and TCR/BCR V(D)J sequencing. The sequencing data revealed SARS-CoV-2-specific shuffling of adaptive immune repertories and COVID-19-induced remodeling of peripheral lymphocytes.

Characterization of variations in the peripheral T and B cells from the COVID-19 patients revealed a positive correlation of humoral immune response and T-cell immune memory with disease severity. Sequencing and functional data revealed SARS-CoV-2-specific T-cell immune memory in the convalescent COVID-19 patients. Furthermore, we also identified novel antigens that are responsive in the convalescent patients. Altogether, our study reveals adaptive immune repertories underlying pathogenesis and recovery in severe versus mild COVID-19 patients, providing valuable information for potential vaccine and therapeutic development against SARS-CoV-2 infection.

Reference

Zhang, Fan, Rui Gan, Ziqi Zhen, Xiaoli Hu, Xiang Li, Fengxia Zhou, Ying Liu et al. "Adaptive immune responses to SARS-CoV-2 infection in severe versus mild individuals." *Signal Transduction and Targeted Therapy* 5, no. 1 (2020): 1-11 (I.F.: 13.493).

Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets

Abstract

Chest CT is emerging as a valuable diagnostic tool for clinical management of COVID-19 associated lung disease. Artificial intelligence (AI) has the potential to aid in rapid evaluation of CT scans for differentiation of COVID-19 findings from other clinical entities. Here we show that a series of deep learning algorithms, trained in a diverse multinational cohort of 1280 patients to localize parietal pleura/lung parenchyma followed by classification of COVID-19 pneumonia, can achieve up to 90.8% accuracy, with 84% sensitivity and 93% specificity, as evaluated in an independent test set (not included in training and validation) of 1337 patients. Normal controls included chest CTs from oncology, emergency, and pneumonia-related indications. The false positive rate in 140 patients with laboratory confirmed other (non COVID-19) pneumonias was 10%. AI-based algorithms can readily identify CT scans with COVID-19 associated pneumonia, as well as distinguish non-COVID related pneumonias with high specificity in diverse patient populations.

Reference

Harmon, Stephanie A., Thomas H. Sanford, Sheng Xu, Evrim B. Turkbey, Holger Roth, Ziyue Xu, Dong Yang et al. "Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets." *Nature Communications* 11, no. 1 (2020): 1-7 (I.F.: 12.121).

Implications of sex differences in immunity for SARS-CoV-2 pathogenesis and design of therapeutic interventions

Abstract

Men present more frequently with severe manifestations of COVID-19 and are at higher risk for death. The underlying mechanisms for these differences between female and male individuals infected with SARS-CoV-2 are insufficiently understood. However, studies from other viral infections have shown that females can mount stronger immune responses against viruses than males. Emerging knowledge on the basic biological pathways that underlie differences in immune responses between women and men needs to be incorporated into research efforts on SARS-CoV-2 pathogenesis and pathology to identify targets for therapeutic interventions aimed at enhancing antiviral immune function and lung airway resilience while reducing pathogenic inflammation in COVID-19.

Reference

Bunders, Madeleine, and Marcus Altfeld. "Implications of sex differences in immunity for SARS-CoV-2 pathogenesis and design of therapeutic interventions." *Immunity* 1920 (2020) (IF: 21.522).

Publication Date: Aug 13, 2020

Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study

Abstract

Background: Diabetes has been associated with increased COVID-19-related mortality, but the association between modifiable risk factors, including hyperglycaemia and obesity, and COVID-19-related mortality among people with diabetes is unclear. We

assessed associations between risk factors and COVID-19-related mortality in people with type 1 and type 2 diabetes.

Methods: We did a population-based cohort study of people with diagnosed diabetes who were registered with a general practice in England. National population data on people with type 1 and type 2 diabetes collated by the National Diabetes Audit were linked to mortality records collated by the Office for National Statistics from Jan 2, 2017, to May 11, 2020. We identified the weekly number of deaths in people with type 1 and type 2 diabetes during the first 19 weeks of 2020 and calculated the percentage change from the mean number of deaths for the corresponding weeks in 2017, 2018, and 2019. The associations between risk factors (including sex, age, ethnicity, socioeconomic deprivation, HbA1c, renal impairment [from estimated glomerular filtration rate (eGFR)], BMI, tobacco smoking status, and cardiovascular comorbidities) and COVID-19-related mortality (defined as International Classification of Diseases, version 10, code U07.1 or U07.2 as a primary or secondary cause of death) between Feb 16 and May 11, 2020, were investigated by use of Cox proportional hazards models.

Findings: Weekly death registrations in the first 19 weeks of 2020 exceeded the corresponding 3-year weekly averages for 2017–19 by 672 (50·9%) in people with type 1 diabetes and 16 071 (64·3%) in people with type 2 diabetes. Between Feb 16 and May 11, 2020, among 264 390 people with type 1 diabetes and 2 874 020 people with type 2 diabetes, 1604 people with type 1 diabetes and 36 291 people with type 2 diabetes died from all causes. Of these total deaths, 464 in people with type 1 diabetes and 10 525 in people with type 2 diabetes were defined as COVID-19 related, of which 289 (62·3%) and 5833 (55·4%), respectively, occurred in people with a history of cardiovascular disease or with renal impairment (eGFR <60 mL/min per 1·73 m2). Male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19-related mortality in both type 1 and type 2 diabetes. Compared with people with an HbA1c of 48–53 mmol/mol (6·5–7·0%), people with an HbA1c of 86 mmol/mol (10·0%) or higher had increased COVID-19-related mortality (hazard ratio [HR] 2·23 [95% CI 1·50–3·30, p<0·0001] in type 1 diabetes and 1·61 [1·47–1·77, p<0·0001] in type 2 diabetes). In addition, in people with type 2 diabetes, COVID-19-related mortality was significantly higher in those with an HbA1c of 59 mmol/mol (7·6%) or higher than in those with an

HbA1c of 48–53 mmol/mol (HR 1·22 [95% CI 1·15–1·30, p<0·0001] for 59–74 mmol/mol [7·6–8·9%] and 1·36 [1·24–1·50, p<0·0001] for 75–85 mmol/mol [9·0–9·9%]). The association between BMI and COVID-19-related mortality was U-shaped: in type 1 diabetes, compared with a BMI of 25·0–29·9 kg/m2, a BMI of less than 20·0 kg/m2 had an HR of 2·45 (95% CI 1·60–3·75, p<0·0001) and a BMI of 40·0 kg/m2 or higher had an HR of 2·33 (1·53–3·56, p<0·0001); the corresponding HRs for type 2 diabetes were 2·33 (2·11–2·56, p<0·0001) and 1·60 (1·47–1·75, p<0·0001).

Interpretation: Deaths in people with type 1 and type 2 diabetes rose sharply during the initial COVID-19 pandemic in England. Increased COVID-19-related mortality was associated not only with cardiovascular and renal complications of diabetes but, independently, also with glycaemic control and BMI.

Reference

Holman, Naomi, Peter Knighton, Partha Kar, Jackie O'Keefe, Matt Curley, Andy Weaver, Emma Barron et al. "Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study." *The Lancet Diabetes & Endocrinology* (2020) (I.F.: 25.34).

Clinical characteristics and corticosteroids application of different clinical types in patients with corona virus disease 2019

Abstract

To describe the epidemiological and clinical characteristics of patients with Corona Virus Disease 2019 (COVID-19) in Beijing. To analyze the application of corticosteroids in patients with severe pneumonia. We collected information on demographic characteristics, exposure history, clinical characteristics, corticosteroids use, and outcomes of the 65 confirmed cases of COVID-19 at Fifth Medical Center of PLA General Hospital from Jan 20 to Feb 23, 2020. The final follow-up date observed was April 15th, 2020. The number of patients with mild, general, severe, and critical type were 10 (15.38%), 32 (49.23%), 8 (12.31%), and 15 (23.08%), respectively. The median incubation period was 6 days. Notable outliers were 1 patient at 16 days and 1 patient at 21 days. In lymphocyte subgroup analysis, decreases in total, T, CD4, and CD8 lymphocytes were more common as the disease worsened (All $P < 0.05$).

Methylprednisolone (mPSL) was applied to 31 (47.69%) patients with pneumonia, including 10 (31.25%) general, 8 (100%) severe, and 13 (86.67%) critical patients, respectively. Corticosteroids inhibited Interleukin-6(IL-6) production ($P = 0.0215$) but did not affect T lymphocyte ($P = 0.0796$). There was no significant difference between patients using lower dose (≤ 2 mg/kg day) and higher dose (> 2 mg/kg day) mPSL in inhibiting IL-6 production ($P = 0.5856$). Thirty of 31 patients (96.77%) had stopped mPSL due to improvement of pneumonia. Virus RNA clearance time lengthened with disease progression ($P = 0.0001$). In general type, there was no significant difference in virus clearance time between patients with (15, 12–19 days) and without (14.5, 11–18 days) ($P = 0.7372$) mPSL use. Lymphocyte, especially T lymphocyte, in severe and critical patients showed a dramatic decrease. Application of lower dose corticosteroids (≤ 2 mg/kg day) could inhibit IL-6 production (a representative of cytokines) as effectively as a higher dose. Proper use corticosteroids in general type patients did not delay virus clearance.

Reference

Liu, Fangfang, Chengcheng Ji, Jiajun Luo, Weiwei Wu, Junchang Zhang, Zhiqiang Zhong, Seth Lankford et al. "Clinical characteristics and corticosteroids application of different clinical types in patients with corona virus disease 2019." *Scientific Reports* 10, no. 1 (2020): 1-9 (I.F.: 3.998).

PREVIEW

Publication Date: Aug 18, 2020

Interferon-λ at the Center of the Storm

A hallmark of successful host restriction of viral infection is the rapid induction of interferons (IFNs) to initiate innate and adaptive immunity. Type I (IFN-α/β) and type III (IFN-λ1–4) IFNs exert collaborative antiviral effects on cells by inducing transcription of hundreds of antiviral IFN-stimulated genes (ISGs) to promote viral clearance. Type I and III interferons (IFNs) drive effective antiviral functions but differentially affect tissue homeostasis. Using mouse models of severe inflammation, Broggi *et al.* and Major *et al.* report in Science that type III IFNs disrupt epithelial cell proliferation and differentiation in the lung. For more details, read the link given below.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(20)30331-9

Publication Date: Aug 19, 2020

Coronavirus research updates: An unprecedented map charts a key viral protein

An unprecedented map charts a key viral protein (19 August 2020):

For the first time, researchers have mapped the 3D shape of spike proteins that are part of intact SARS-CoV-2 particles.

Spike proteins decorate the surface of coronaviruses and lock onto host receptors, such as ACE2, to gain entry to cells. The first structures of SARS-CoV-2's spike were gleaned from modified proteins that had been expressed in cells and then purified. To check these models John Briggs at the Medical Research Council Laboratory of Molecular Biology in Cambridge, UK, and colleagues collected viral particles from infected cells and determined the shape of their spike proteins using electron microscopy (Z. Ke et al. Nature http://doi.org/d6sf; 2020).
These structures closely resembled the ones determined from purified forms. In both, the spike protein can adopt either a 'closed' confirmation or an 'open' one, which allows it to bind to a receptor. Studying the structure in viral particles could help to explain how spike-binding antibodies block nfection, the researchers say.

Sailors furnish first evidence that antibodies protect humans against re-infection (17 August 2020):

A massive COVID-19 outbreak on a US fishing boat spared crew members who already had antibodies against the new coronavirus, providing what scientists say is the first direct evidence that these antibodies protect people against being reinfected. After a viral infection, the immune system makes compounds called neutralizing antibodies that can attack the virus if it invades again. But previous research had not determined whether such antibodies can shield humans from SARS-CoV-2 reinfection.

Alexander Greninger at the University of Washington School of Medicine in Seattle and his colleagues tested the crew of a US fishing vessel for SARS-CoV-2 and for

antibodies to the virus (A. Addetia et al. Preprint at medRxiv http://doi.org/d6qm; 2020). Just before the ship's departure, the researchers tested 120 of the 122 crew members and found that all were negative for SARS-CoV2, but an outbreak hit the ship soon after it left shore. Post-voyage testing showed that 104 members of the 122-person crew were infected. None of those who were infected and had been tested before embarking had shown neutralizing antibodies against SARS-CoV-2.

But all three crew members who did have such antibodies before departure escaped infection, providing statistically significant evidence that neutralizing antibodies acquired during SARS-CoV-2 infection protect against reinfection, the authors say. The findings have not yet been peer reviewed.

Reference

https://www.nature.com/articles/d41586-020-00502-w

Evidence lags behind excitement over blood plasma as a coronavirus treatment

A Researchers call for more rigorous clinical trials as rumours abound that US regulators are considering widening access to the potential therapy.

US President Donald Trump has called on COVID-19 survivors to donate their blood plasma as a treatment for the disease, saying that "it's had tremendous response so far". Meanwhile, rumours have been swirling that US drug regulators are grappling with whether to give the plasma to more people by authorizing it as an emergency therapy. But researchers and clinicians around the world are concerned that a push to distribute blood plasma could undermine the clinical trials needed to determine whether it actually works against COVID-19.

Although some US hospitals already offer the treatment in special cases, an emergency-use authorization from the Food and Drug Administration (FDA) would make it easier to obtain and administer convalescent plasma — the yellow liquid that remains after cells are removed from blood. But so far, there's little evidence that plasma actually helps patients, and the decision could confound efforts to study its effects, says former FDA commissioner Robert Califf, who now heads clinical policy and strategy at Verily and Google Health in South San Francisco, California. The antiviral drug

remdesivir and the anti-inflammatory medicine dexamethasone are the only treatments that have been shown to combat COVID-19 in rigorous clinical trials. For more details, read the link given below.

Reference

https://www.nature.com/articles/d41586-020-02324-2

NIH imposes 'outrageous' conditions on resuming coronavirus grant targeted by Trump

The National Institutes of Health is requiring a small nonprofit research organization to take unusual—and perhaps impossible—steps to end a controversial suspension of an NIH grant related to bat coronavirus research in China. NIH's conditions for reinstating the funding to the EcoHealth Alliance are "outrageous," former NIH Director Harold Varmus told The Wall Street Journal (WSJ) in an article published today that first reported the agency's demands.

The controversy began in April, after President Donald Trump complained about NIH's grant to the EcoHealth Alliance because it involved researchers at China's Wuhan Institute of Virology (WIV). Conservative commentators, Trump, and Trump administration officials have asserted, without evidence, that the novel coronavirus that causes COVID-19 escaped from WIV. Shortly after Trump's complaint, NIH abruptly canceled the grant, stating that its goal of studying bat coronavirus spillovers into humans did not "align with … agency priorities." NIH's move drew extensive criticism from the scientific community.

Last month, NIH Deputy Director for Extramural Research Michael Lauer sent the EcoHealth Alliance a letter stating the agency was reinstating the grant, but also instantly suspending it again pending the completion of certain actions. For more details, read the link given below.

Reference

https://www.sciencemag.org/news/2020/08/nih-imposes-outrageous-conditions-resuming-coronavirus-grant-targeted-trump#

Drap approves clinical trial of Covid-19 vaccine

According to a document, signed by Drap Clinical Studies Committee secretary Shafqat Hussain Danish, and available with Dawn, the committee recommended that the trial be held in Indus Hospital, Karachi. This test will be carried out by the International Centre for Chemical and Biological Sciences, Karachi, in collaboration with a Chinese company already conducting trials in China.

As many as 200 volunteers from Karachi, representing various ethnic groups, have been registered. The trial will be completed in 56 days during which three injections of inactivated virus will be administered to the volunteers — both male and female.

Minister for Planning, Development and Special Initiatives Asad Umar, who also heads the National Coordination and Operation Centre on Covid-19, said he was hopeful that the trials on the vaccine would be successful. If this trial is successful, the vaccine will be easily available to us at affordable rates.

The phase-III clinical trial is designed to evaluate whether an investigational vaccine can prevent symptomatic Covid-19 among adults.

On March 24, Minister for Science and Technology Fawad Chaudhry had constituted a committee — Scientific Task Force on Covid-19 — which was headed by renowned scientist Prof Dr Attaur Rehman. Its other members are University of Health Sciences Vice Chancellor Prof Dr Javed Akram, Dr Ghazna Khalid, Prof Al Fareed Zafar, Prof Iqbal Chaudhry, Prof Dr Khalid Khan and Prof Mariam Riaz Tarar.

One of the committee members said that the trial will be commenced from next week, which will be participated by 200 volunteers (from various ethnic groups, all over 18 years of age) to analyse their results. For this, Karachi is the most appropriate city as people from all backgrounds are settled there. Also, vaccine showed a good safety profile, with few side effects (mild fever, tiredness, headache or allergy), which every medicine has in one per cent cases.

This trial will build a positive image of Pakistan. Meanwhile, according to a statement issued by the National Institute of Health (NIH), this would be the first-ever phase-III clinical trial for any vaccine in Pakistan. For more details, read the link given below.

Reference

https://www.dawn.com/news/1575014/drap-approves-clinical-trial-of-covid-19-vaccine

Publication Date: Aug 17, 2020

NIH obtains formal approval from regulatory body for Phase III clinical trial of Covid-19 vaccine

The National Institute of Health (NIH) said on Monday that it had obtained formal approval from the Drug Regulatory Authority of Pakistan (Drap) for the Phase III clinical trial of a Covid-19 vaccine developed by CanSinoBio, a China-based vaccine developer, and the Beijing Institute of Biotechnology. It is a tripartite activity between NIH, CanSinoBio and AJM Pharma. The study will be conducted in prestigious medical centres in the country, including the Aga Khan Medical University and the Indus Hospital in Karachi, the Shaukat Khanum Memorial Hospital and the University of Health Sciences in Lahore and the Shifa International Hospital in Islamabad.

In a statement, NIH said that this will be the first ever phase III clinical trial for any vaccine in Pakistan. "It is a multi-country, multi-centre clinical trial being conducted by CanSinoBio already in China, Russia, Chile, Argentina and shortly in Saudi Arabia."

The statement added that the principal investigator of the clinical trial would be Major General Aamer Ikram, who is the NIH executive director, adding that the AJM Pharma chief executive officer, Adnan Hussain, had signed an agreement with the institute last month for collaborating on the clinical trial of the vaccine, known as recombinant novel coronavirus vaccine adenovirus type 5 vector (Ad5-nCoV).

The National Bioethics Committee (NBC) of the Pakistan Health Research Council (PHRC) has given ethical approval for the study while the clinical trial has also been approved by the highest global regulatory body. Being a part of this activity, Pakistan

will be among the priority countries to have early access for the Covid-19 vaccine through NIH. For more details, read the link given below.

Reference

https://www.dawn.com/news/1574929/nih-obtains-formal-approval-from-regulatory-body-for-phase-iii-clinical-trial-of-covid-19-vaccine

POLICY FORUM

Publication Date: Aug 13, 2020

Knowledge transfer for large-scale vaccine manufacturing

As the world rushes to identify safe and effective vaccines and therapeutics to counter the coronavirus disease 2019 (COVID-19) pandemic, attention is turning to the next step: manufacturing these products at enormous scale. To speed up the process, firms are even establishing manufacturing capacity "at risk," before products receive regulatory approval. Yet for at least some complex COVID-19 vaccines and biological therapeutics, fast manufacturing, particularly of products originally developed by other firms, will require not only physical capacity but also access to knowledge not contained in patents or in other public disclosures; one reason for the expense and delay historically associated with entry of biosimilars into the market has been the cost and time associated with reverse engineering originator firms' manufacturing processes. But a change may be coming. A group of six biopharmaceutical firms researching monoclonal antibody (mAb) candidates recently sought [and the U.S. Department of Justice (DOJ) granted] permission under antitrust law to exchange "technical information" on each other's manufacturing processes and platforms (but not information on cost or price). A focus on rapid information exchange of the sort recently encouraged by the DOJ will not only be critical for the current crisis but could also create the foundation for fewer siloes, improved standardization, and less secrecy over manufacturing information in the future. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/early/2020/08/12/science.abc9588/tab-e-letters