BIOENGINEERING

Membrane Nanoparticles Derived from ACE2-Rich Cells Block SARS-CoV-2 Infection

Wang et al. introduce a potential treatment for COVID-19 based on the fundamental characteristics of viral spike proteins and receptor binding. ACE2 is the well-known receptor of SARS-CoV-2 which allows it to enter the host cells. Wang et al. engineered membrane nanoparticles (ACE2-NPs) from ACE2-rich cells designed to suppress viral infection by competitive inhibition through binding the spike proteins of SARS-CoV-2. The ACE2-NPs demonstrated an inhibitory effect on the S1, which is a subunit of spike protein that recognizes the host receptors. Incubation of HK-2 human renal tubular epithelial cells with S1, with and without the presence of ACE2-NPs, showed a significant decrease in S1 receptor recruitment to cells. To test a more infectious case, an S1 variant was prepared by a single site mutation and resulted in a comparable affinity to ACE2 (11.6nM) compared to the wild-type S1 which has an affinity of (8.02nM). Also, ACE2-NPs treatment had a suppressive effect on the S1-induced apoptosis by increasing Optic atrophy 1 (OPA1) expression which is responsible for apoptosis by inhibiting the cytochrome c release. The antiviral activity of ACE2-NPs in various organs was verified using an in vivo mouse model—tracking the differently tagged ACE2 and S pseudovirions.

Sensitive quantitative detection of SARS-CoV-2 in clinical samples using digital warm-start CRISPR assay

RT-PCR has been the main technology used to detect SARS-CoV-2. However, its widespread use is limited by its reliance on PCR machines and the reliability of hydrolysis probes used. To address this issue, researchers from the University of Connecticut Health Center explored CRISPR-Cas as a detection method to identify nucleic acids that indicate the presence of COVID-19 in a sample. Although current CRISPR systems in use, (DETECTR and SHERLOCK) are effective, they require multiple steps. The researchers modified this by creating the digital warm-start CRISPR assay (dWS-CRISPR), a one-pot quantitative test. As one of its key features, the “warm-start” assay requires temperatures above 50°C to start—so that amplification cannot begin before the desired time frame. It is prepared by combining RT-DAMP primers, Cas RNA complexes, and other components and then coating the solution onto a digital chip. When incubated with a positive COVID-19 sample, quantifiable fluorescence will visibly appear due to reaction with the target RNA and thus confirm detection of SARS-CoV-2 nucleic acids. The researchers also compared two Cas12a nucleases and determined that the A.s. Cas12a nuclease was the best choice for the assay due to its greater cleavage activity at the lower Mg²⁺ concentrations needed to boost amplification. Additionally, the dWS-CRISPR assay is an improvement upon the non-digital WS-CRISPR assay, and was shown to be more effective due its use of a chip that is typically only used for digital PCR tests. The dWS-CRISPR’s high sensitivity and visible fluorescence allows for relatively simple sample reading, can be effectively used with saliva samples, and can be optimized for broader use by medical professionals.
Scalable, methanol-free manufacturing of the SARS-CoV-2 receptor binding domain in engineered Komagataella phaffii

Microorganisms such as Komagataella phaffii (Pichia pastoris) are commonly used in the large-scale manufacturing of proteins and enzymes for biotherapeutic purposes. Researchers from the Love group at the Koch Institute at MIT report a scalable technique which uses an engineered Komagataella phaffii platform to produce receptor binding domain (RBD) proteins, which are expressed on SARS-CoV-2 S proteins and are used as antigens in multiple SARS-CoV-2 vaccine candidates. The manufacturing method developed here does not require the use of methanol to induce bacterial metabolic processes, which simplifies manufacturing and reduces flammability risk. Instead, they integrated additional copies of endogenous transcription factors mit1 and mxr1 to allow constitutive overexpression of the recombinant gene in the presence of sorbitol. In general, this methanol-free manufacturing scheme resulted in a 3- to 5-fold increase in productivity of these engineered strains. The group hypothesizes that this improved productivity is possibly because sorbitol-fed mit1+ strains exhibit less protein folding stresses during RBD transcription. The group compared manufacturing of both the methanol- and sorbitol-induced yeast using their InSCyT biomanufacturing platform—finding that the sorbitol-induced yeast exhibited sustained RBD production with less cellular stress and fewer impurities than the base strain. They then demonstrated that they could scale up to liter scale cultures in a bioreactor, and that the mit1+ cells were capable of producing RBD variants.*

* Please note all studies published in medRxiv and bioRxiv are preprints and have not yet undergone a rigorous peer review process.

CLINICAL PRESENTATION AND MANAGEMENT

Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection*

INTERCOVID was a prospective cohort study carried out in 43 institutions and 18 countries to assess the impact of COVID-19 on maternal and neonatal outcomes. Between March and October 2020, 706 pregnant women with a COVID-19 diagnosis were recruited. For each subject with a diagnosis, two controls (pregnant women of similar gestational age but without a COVID-19 diagnosis) were enrolled. Compared to the pregnant women without COVID-19, those with COVID-19 had 1.46 higher rates of pregnancy-induced hypertension (1.05-2.02), 1.76 higher rates of preeclampsia/eclampsia (1.27-2.43), and 3.38 higher rates of infections requiring antibiotics (1.63-7.01). COVID-19 diagnosis was also associated with a 5.04 greater risk of ICU admission (3.13-8.10), and, among those admitted to the ICU, those with COVID-19 stayed 3.73 days (2.37-5.86) longer than those without. The relative risk of death was 22.3 times as high for mothers with COVID (2.88-172). Mothers with COVID-19 also delivered about a week earlier. The risk of neonates having at least one of several morbidities was 2.66 (95% 1.69-4.18) higher in those born of women with COVID-19. Cesarean delivery was the only factor associated with SARS-CoV-2 infection among neonates (ie not breastfeeding. Overall, this study shows the significantly heightened risk of mortality and several morbidities among pregnant women and neonates who become infected with COVID-19.
NON-CLINICAL TRENDS

Impact of COVID-19 on routine immunization in South-East Asia and Western Pacific: Disruptions and solutions

Harris et al. examined disruptions in routine immunizations caused by the COVID-19 pandemic in Southeast Asia and Western Pacific (SEA/WP) regions. A questionnaire was administered to 19 countries between June 14 and July 10, 2020, to evaluate the status of routine immunizations between February/March 2020 and June 1, 2020. Overall, 95% of countries in SEA/WP experienced vaccination disruption. Countries reported a median of 15 antigens for which immunizations have been disrupted due to COVID-19, with infants and school-entry age children experiencing the most disruption in their routine vaccination schedule. Middle-income countries experienced higher rates of disruption than high-income countries. Patients’ fear of infection, travel restrictions, and lack of healthcare access were frequently cited as reasons for vaccine disruption (100%, 88%, and 76%, respectively). The authors proposed several solutions to mitigate disruption, including virtual engagement and awareness campaigns, creating a dedicated immunization space that excludes sick/infectious patients, and offering home vaccination services.

MODELS

Modelling COVID-19 transmission in supermarkets using an agent-based model

Supermarkets are considered one of the main hubs that congregate large groups of people. Ying et al. quantitively assessed mitigation efforts to reduce COVID-19 virus transmission in supermarkets. An agent-based model was applied to shopping data and a synthetically created store layout with $10^6$ paths. The model consisted of two components, a customer mobility model and a virus transmission model, to estimate exposure time and infections due to human-to-human contact. After 1000 iterations, the results showed that an average of 14.96 customers were present in the supermarket at a given time and spent an average 5.97 minutes in the store. Total exposure time was average 94.98 minutes per day and the longest exposure time in the simulation was 3.5 minutes. Restrictions on the maximum number of customers in the store, reduced customer arrival rate, using face masks, and a one-way aisle layout were added to the simulation to measure the varying risk of transmission and identify hotspots and bottlenecks. This model can be implemented for other settings to inform best policies for other retail stores with varying network features and sizes, to measure virus transmission and reduce spread.

MENTAL HEALTH

A looming mental health pandemic in the time of COVID-19? Role of fortitude in the interrelationship between loneliness, anxiety, and life satisfaction among young adults

Pretorius et al. investigated the impact of COVID-19 pandemic and lockdown on mental health. They examined the relationship between life satisfaction, anxiety, and loneliness in relation to fortitude, or ability to manage stress, among 332 randomly sampled young South African adults from a university in the Western Cape Province. Each participant completed four questionnaires (UCLA Loneliness Scale, State-Trait Anxiety Scale, Satisfaction with Life scale, Fortitude Questionnaire) throughout the lockdown period between March – June
The mean score for loneliness was 49.1 (71.8% of the students to be considered lonely) and for anxiety was 48.1 (73.3% considered to have high anxiety), both of which were higher than in previous studies. Life satisfaction was reported as 20.0, also lower than previous means, indicating that the pandemic impacted and diminished respondents’ feeling of life satisfaction. Statistically significant differences between men and women were found with men reporting lower mean loneliness and anxiety scores than women. Fortitude had no moderating effect in the relationship between loneliness and anxiety, however loneliness was reported to be associated with fortitude. These results indicate that predictor variables of loneliness and anxiety mediate the effect of fortitude on the outcome variables. These findings are critical to guide the public health response to address the mental health consequences of the pandemic. This study can serve as useful platform to support future research about mental health and the impact of COVID-19 in sub-Saharan Africa and other countries.

**PEDIATRIC PRESENTATION**

**Simulated Identification of Silent COVID-19 Infections Among Children and Estimated Future Infection Rates With Vaccination**

Given that children can serve as significant sources of silent COVID-19 transmission (pre-symptomatic or asymptomatic) and that they can’t yet receive COVID-19 vaccines, Moghadas et al conducted a simulation to understand infection identification strategies needed among children to suppress future population outbreaks. Assuming 40% vaccine coverage among adults, an effective reproduction number of 1.2, and a population of similar demographics to that of the US, the authors analyzed the proportion of silent COVID-19 infections among children that would need to be identified and the speed at which it would be required to maintain an overall attack rate of less than 5%. Based on these parameters, identification of at least 11% of silent infections among children within two days of infection would be necessary to maintain a population attack rate ≤ 5%. A greater proportion of infections would need to be identified if done with a greater delay (14% within three days or 41% within four days) to reach the same target. If efforts are not implemented to identify silent infections among children, a 10.8% population attack rate (95% CI 10.5–11.2%) will result. In order to maintain a 5% overall attack rate and not detect any silent infections among children, at least 81% of children – in addition to the 40% of adults – would need to be vaccinated. Given that such high vaccination rates among children are unlikely to be reached soon, targeted interventions to identify silent infections among children are required to prevent future outbreaks.

**PHARMACEUTICAL INTERVENTION**

**Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients — United States, April 2021**

On April 13, 2021 the CDC and the FDA recommended pausing use of the Janssen single dose vaccine upon reports of thrombocytopenia syndrome (TTS) after vaccination. As of April 21, 2021, there have been an estimated 7.98 million doses of Janssen vaccine distributed in the United States and 15 reported cases of rare blood clotting post-vaccination (with 12 cases presenting with TTS). All 15 cases were women, 13 were
between the ages of 18 and 49, 2 were in women older than 50, and 3 have died. The Advisory Committee on Immunization Practices (ACIP) created a risk-benefit analysis on both a population- and individual-level to determine whether the Janssen vaccine is safe for continued use. The population-level analysis predicted that with 6 months of Janssen’s continued use for people older than 18, 3,926-9,395 hospitalizations, 928-2,236 ICU admissions, and 586-1,435 deaths due to COVID could be avoided, with an expected 26 cases of TTS. For those older than 50, 1,361-3,532 hospitalizations, 295-799 ICU admissions, and 54-257 deaths could be avoided, with an expected 2 cases of TTS. Similar to the population-level analysis, the individual-level analysis showed that the benefits gained from vaccinations far outweighed the risks. So, on April 23, 2021 the ACIP reaffirmed that the vaccine could be used for people over 18. However, the FDA added a warning to the emergency use authorization (EUA), to be provided to all patients and caregivers, that there is a risk of rare clotting events.

Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study

Vasileiou et al conducted a prospective cohort study to investigate the association between the COVID vaccine roll-out and hospital admissions due to COVID in Scotland. They used a dataset that contained vaccination, primary care, laboratory testing, hospital admission, and mortality data for people averaging 65 years of age. The study included data from December 8, 2020 to February 22, 2021, with participants receiving either the first dose of Pfizer-BioNTech or Oxford-AstraZeneca. During the study period, 1,331,993 people, or about 30% of adults 18 years and older, received the first dose. 28 to 34 days after receiving the first shot, Pfizer and Oxford showed 91% and 88% vaccine efficacy, respectively (defined as reduced hospital admissions). People of lower socioeconomic status and those who lived in large urban regions had lower vaccination rates, and increased vaccination rates correlated with an increase in the number of comorbidities. Overall, the first doses of the vaccines were successful in reducing hospital admission due to COVID-19.

TRANSMISSION PATTERNS

Comparison of COVID-19 incidence rates before and after school reopening in Israel

Somekh et al. investigated the relationship between schools reopening and COVID-19 incidence rates for children aged 0-9 in Israel. Incidence of SARS-CoV-2 infection was measured between August and December 2020, when schools in Israel were reopened and subsequently closed. During school attendance periods in September and November, children aged 0-9 had lower rates of incidence rate ratios (IRR 1.1 and 1.34, respectively) and test positivity rate ratios (RR 0.77 and 0.75) compared to children age 10-19 (IRR 3.1 and 1.9; RR 1.5 and 0.97). The authors suggest that children age 0-9 did not significantly contribute to the national surge in COVID-19 cases or SARS-CoV-2 transmission in September 2020.
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References:


