2020-10-19

Welcome to Week 31!!

I'm still stuck on a rock theme to start off the week. Steve Winwood started his rock career at the age of 14 when he joined the Spencer Davis Group. One of the great songs of my college years was 'Gimme Some Lovin'' which Winwood co-wrote. He left to form Traffic and formed a super group along with Eric Clapton, Ginger Baker and Ric Grech. It is so cool to see Winwood still rocking things in this 'COVID-19 pandemic' version of 'Gimme Some Lovin': https://www.youtube.com/watch?v=rpkqTLR3OD8 For contrast here is the group in Finland from 1967: https://www.youtube.com/watch?v=xcxYX8KPhGk and how about this from 1986 on Letterman with 'Higher Love' and 'Gimme Some Lovin': https://www.youtube.com/watch?v=YOAhl1ocaoM How cool are these clips?

The New York Times covers a Salt Lake City high school that had one of the biggest coronavirus outbreaks in the state. This is indeed a cautionary tale and points out the difficulty of minimizing COVID-19 in schools. Interestingly, the affected schools were mainly high schools and one middle school. HHS Secretary Azar says treatments are weeks away. That may be so, but the monoclonal antibody therapies will have to be rationed as production is not fully ramped up. One bright light is that some patients appear to recover from COVID-19 lung damage! Yes, China is an authoritarian state and able to impose lockdowns but they are getting their economy back on track. New York City schools have seen a very low positive test rate for COVID-19. Let's hope this continues.

The Washington Post has an op-ed by former CDC director Tom Frieden opposing the herd immunity approach. Here is a not so kind story about the inside workings of the Administration's Coronavirus Task Force. Read the article, I'm not saying anything further. There is a debate about the safety of flying; no surprise here. Contact tracing has worked in this Arizona Apache Tribe. Tony Fauci weighs in on 60 Minutes.

STAT have a poll on American's interest in getting a COVID-19 vaccination. Here is an opinion piece on the White House superspreader convocation.

MODELING

- Background: Many rural hospitals and health systems in the U.S. lack sufficient resources to treat COVID-19. We developed a system for managing inpatient COVID-19 hospital admissions in St. Lawrence County, an underserved rural county which is the largest county in New York State. Methods: We used a hub and spoke system to route COVID-19 patients in the St. Lawrence Health System to its flagship hospital. We assembled a small clinical team to manage admitted COVID-19 patients and to stay abreast of a quickly changing body of literature and standard of care. We subsequently completed a review of clinical data for patients who were treated by our inpatient COVID-19 treatment team between March 20 and May 22, 2020. Results: Twenty COVID-19 patients were identified. Sixteen patients (80%) met NIH criteria for severe or critical disease. One patient died. No patients were transferred to other hospitals. Conclusions: During the first two months of the pandemic, we were able to manage hospitalized COVID-19 patients in our rural community. Development of similar treatment models in other rural areas should be considered. [**note: this is a model used in a large rural county to manage COVID-19. We too often lose sight that there many rural areas of the US that are affected by the pandemic and**

let's hope that these lessons can be transferred on.]
https://www.medrxiv.org/content/10.1101/2020.10.15.20213348v1

- The visualization of viral pathogens in infected tissues is an invaluable tool to understand spatial virus distribution, localization, and cell tropism in vivo. Commonly, virus-infected tissues are analyzed using conventional immunohistochemistry in paraffin-embedded thin sections. Here, we demonstrate the utility of volumetric three-dimensional (3D) immunofluorescence imaging using tissue optical clearing and light sheet microscopy to investigate host-pathogen interactions of pandemic SARS-CoV-2 in ferrets at a mesoscopic scale. The superior spatial context of large, intact samples (> 150 mm^3) allowed detailed quantification of interrelated parameters like focus-to-focus distance or SARS-CoV-2-infected area, facilitating an in-depth description of SARS-CoV-2 infection foci. Accordingly, we could confirm a preferential infection of the ferret upper respiratory tract by SARS-CoV-2 and emphasize a distinct focal infection pattern in nasal turbinates. Conclusively, we present a proof-of-concept study for investigating critically important respiratory pathogens in their spatial tissue morphology and demonstrate the first specific 3D visualization of SARS-CoV-2 infection. [**note: from Germany, here is a 3D reconstruction of SARS-CoV-2 infection in ferrets. Some interesting images in the paper!**]
https://www.biorxiv.org/content/10.1101/2020.10.17.339051v1

NEWLY REGISTERED CLINICAL TRIALS

- Not today, wait until Wednesday.

CLINICAL TRIAL RESULTS

- To date over 36 million people have been infected with the severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). While the vast majority will survive, many may be left with residual effects. Acute neurologic symptoms including encephalitis, acute myopathic quadriplegia, strokes and seizures have been reported in COVID-19.1 Anecdotally, even survivors without acute neurologic conditions have reported long-term neurologic symptoms months after their illness. These reports have called for the importance of studying long-term neurologic outcomes, also referred as the 'Long-Haul COVID'.2 During previous epidemics, including SARS and MERS, both short- and long-term neurological symptoms were reported3 but the chronic neurological symptoms of COVID-19 are unknown. To characterize long-term neurologic outcomes after COVID-19 we followed a cohort of hospitalized patients and assessed 3-months outcomes. [**note: here is a three month neurological study in hospitalized COVID-19 patients from Texas. They ended up with 48 out of 140 that were enrolled in the study. All the follow ups were done by phone because of the pandemic. You will have to download the paper to see the results as the abstract doesn't say much. We need more of this data.**]
https://www.medrxiv.org/content/10.1101/2020.10.16.20211029v1
- There is a major concern regarding the prognosis of coronavirus disease 2019 (COVID-19) in patients who recovered to first-time illness. Objective: To evaluate factors predicting severe symptomatic laboratory-confirmed (reverse transcription-quantitative polymerase chain reaction, RT-qPCR) SARS-COV-2 (severe acute coronavirus-2) reinfection. Method: *We conducted a nationwide retrospective cohort study in Mexico and data from 258 reinfection cases (at least 28 days between both episodes onset) were analyzed.* We used risk ratios (RR)

and 95% confidence intervals (CI) to evaluate predictors of severe (dyspnea requiring hospital admission) secondary SARS-COV-2 infection. Results: The risk of severe disease was 14.7% and the observed overall fatality rate was 4.3%. Patients with more serious primary disease were more likely to develop severe symptoms (39.5% vs. 5.5%, p < 0.001) during reinfection. In multiple analysis, factors associated with an increased risk of severe symptomatic SARS-COV-2 reinfection were increasing age (RR per year = 1.007, 95% CI 1.003-1.010), comorbidities (namely obesity [RR = 1.12, 95% CI 1.01-1.24], asthma [RR = 1.26, 95% CI 1.06-1.50], type 2 diabetes mellitus [RR = 1.22, 95% CI 1.07 - 1.38] and previous severe laboratory-confirmed COVID-19 (RR = 1.20, 95% CI 1.03-1.39). Conclusions: To the best of our knowledge this is the first study evaluating disease outcomes in a large set of laboratory-positive cases of symptomatic SARS-COV-2 reinfection and factors associated with illness severity was characterized. Our results may contribute to the current knowledge of SARS-COV-2 pathogenicity and to identify populations at increased risk of a poorer outcome after reinfection. [**note: this is from Mexico and looks at patients who have laboratory-confirmed SARS-CoV-2 reinfection. This shows a lot more reinfection than I have seen in other studies.**] https://www.medrxiv.org/content/10.1101/2020.10.14.20212720v1

- Respiratory distress requiring intubation is the most serious complication associated with coronavirus disease 2019 (COVID-19).
 Methods In this retrospective study, we used survival analysis to determine whether or not mortality following intubation was associated with hormone exposure in patients treated at New York Presbyterian/ Columbia University Irving Medical Center. Here, we report the overall hazards ratio for each hormone for exposure before and after intubation for intubated and mechanically ventilated patients.
 Results Among the 189,987 patients, we identified 948 intubation periods across 791 patients who were diagnosed with COVID-19 or infected with SARS-CoV2 and 3,497 intubation periods across 2,981 patients who were not. Melatonin exposure after intubation was statistically associated with a positive outcome in COVID-19 (demographics and comorbidities adjusted HR: 0.131, 95% CI: 7.76E-02 - 0.223, *p*-value = 8.19E-14) and non-COVID-19 (demographics and comorbidities adjusted HR: 0.278, 95% CI: 0.142 - 0.542, *p*-value = 1.72E-04) intubated patients. Additionally, melatonin exposure after intubation was statically associated with a positive outcome in COVID-19 patients (demographics and comorbidities adjusted HR: 0.127, 95% CI: 6.01E-02 - 0.269, *p*-value = 7.15E-08).
 Conclusions Melatonin exposure after intubation is significantly associated with a positive outcome in COVID-19 and non-COVID-19 patients. Additionally, melatonin exposure after intubation is significantly associated with a positive outcome in COVID-19 patients requiring mechanical ventilation. While our models account for many covariates, including clinical history and demographics, it is impossible to rule out confounding or collider biases within our population. Further study into the possible mechanism of this observation is warranted. [**note: here is a study from Columbia Univ that shows melatonin is significantly associated with survival of intubated COVID-19 patients. What is interesting is it seems to also help intubated non-COVID-19 patients. There are trials with this and it is one of the drugs President Trump was given during his hospital stay. I'm interested in the mechanism of this finding.**] https://www.medrxiv.org/content/10.1101/2020.10.15.20213546v1
- Background The medium-term effects of Coronavirus disease (COVID-19) on multiple organ health, exercise capacity, cognition, quality of life and mental health are poorly understood. Methods *Fifty-eight COVID-19 patients post-hospital discharge and 30 comorbidity-matched*

controls were prospectively enrolled for multiorgan (brain, lungs, heart, liver and kidneys) magnetic resonance imaging (MRI), spirometry, six-minute walk test, cardiopulmonary exercise test (CPET), quality of life, cognitive and mental health assessments. Findings At 2-3 months from disease-onset, 64% of patients experienced persistent breathlessness and 55% complained of significant fatigue. On MRI, tissue signal abnormalities were seen in the lungs (60%), heart (26%), liver (10%) and kidneys (29%) of patients. COVID-19 patients also exhibited tissue changes in the thalamus, posterior thalamic radiations and sagittal stratum on brain MRI and demonstrated impaired cognitive performance, specifically in the executive and visuospatial domain relative to controls. Exercise tolerance (maximal oxygen consumption and ventilatory efficiency on CPET) and six-minute walk distance (405±118m vs 517±106m in controls, p<0.0001) were significantly reduced in patients. The extent of extra-pulmonary MRI abnormalities and exercise tolerance correlated with serum markers of ongoing inflammation and severity of acute illness. Patients were more likely to report symptoms of moderate to severe anxiety (35% versus 10%, p=0.012) and depression (39% versus 17%, p=0.036) and significant impairment in all domains of quality of life compared to controls. Interpretation A significant proportion of COVID-19 patients discharged from hospital experience ongoing symptoms of breathlessness, fatigue, anxiety, depression and exercise limitation at 2-3 months from disease-onset. Persistent lung and extra-pulmonary organ MRI findings are common. In COVID-19 survivors, chronic inflammation may underlie multiorgan abnormalities and contribute to impaired quality of life. [**note: here is a post-hospitalization follow up from Oxford. A small number as in the Texas study already noted but this group looks at a number of other factors. We do need to know what the percentage is of those who have lingering symptoms.**] https://www.medrxiv.org/content/10.1101/2020.10.15.20205054v1

DRUG DEVELOPMENT

- Nothing today.

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- The spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mediates host cell entry by binding to angiotensin-converting enzyme 2 (ACE2), and is considered the major target for drug and vaccine development. We previously built fully-glycosylated full-length SARS-CoV-2 S protein models in a viral membrane including both open and closed conformations of receptor binding domain (RBD) and different templates for the stalk region. In this work, multiple μs-long all-atom molecular dynamics simulations were performed to provide deeper insight into the structure and dynamics of S protein, and glycan functions. Our simulations reveal that the highly flexible stalk is composed of two independent joints and most probable S protein orientations are competent for ACE2 binding. We identify multiple glycans stabilizing the open and/or closed states of RBD, and demonstrate that the exposure of antibody epitopes can be captured by detailed antibody-glycan clash analysis instead of a commonly-used accessible surface area analysis that tends to overestimate the impact of glycan shielding and neglect possible detailed interactions between glycan and antibody. Overall, our observations offer structural and dynamic insight into SARS-CoV-2 S protein and potentialize for guiding the design of effective antiviral therapeutics. [**note: here is more information on Spike protein and it's binding properties.**] https://www.biorxiv.org/content/10.1101/2020.10.18.343715v1

DIAGNOSTIC DEVELOPMENT

- Nothing today

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2020-10-20

Today's music selection came from a loyal reader!!! This is the Indie rock/country/pop group case/lang/veirs that was formed in 2013. Three women with wonderful voices who can harmonize the heck out of any song. There was a summer 2016 tour but I've not found anything since then which is a shame because of the music they made. Here is a live session set from that period: https://www.youtube.com/watch?v=AWbAP-pbIkE Here is 'Helpless' from that summer tour: https://www.youtube.com/watch?v=d646z7VNG_M and 'Best Kept Secret' from the Newport Folk Festival: https://www.youtube.com/watch?v=__xLmNUu-zc

The Washington Post has an article on the need for speed in pandemic research and how this upsets the traditional model of peer review. Crises can lead to conspiracy theories; here is how to protect yourself! Some large school systems are opening for in person instruction.👍 I hope this goes smoothly!!! In a move that should please some, The Washington Post reports that the UK will be moving forward with human challenge testing of a COVID-19 vaccine this January. There are no details on what vaccine(s) will be tested. I have commented in the past that while this approach is intriguing, it does not address possible safety issues that require large subjects in trials, nor does it address the needs of older people who likely require a higher dose of the vaccine because they do not have as robust immune systems. I am glad not to be a member of the ethics board that will review this proposal. Singapore is introducing rapid antigen testing for weddings and business conferences. Rapid testing is being offered at London's Heathrow Airport. Older men may be the best plasma donors! This is not entirely unsurprising since men are more susceptible to severe COVID-19 symptoms and such patients generate a stronger antibody response. Here is how HEPA air purifiers can help fight COVID-19 aerosols. I think all schools should have them in buildings to add an extra margin of protection. Do you have money sitting in an airline's account because your travel plans were KOed by the pandemic? California and New York plan to do independent reviews of a COVID-19 vaccine. This is a grade A stupid idea!

The New York Times has a good op-ed from the author of the book on the 1918 flu pandemic about herd immunity and what the proponents are not telling you. Here is the latest news story on this. CDC is recommending wearing masks when on a plane, train, bus or other public transit. Ireland is reimposing a national lockdown. What is happening in Montana pretty much explains why the US is failing at containing COVID-19. Here is an update on Chinese vaccine trials.

I will take an **editorial privilege** and make some comments about herd immunity. Some is this is drawn from my research experience at NIH many years ago. Our lab was looking at some of the lethal factors of *B. pertussis*, aka whooping cough. The vaccine at the time (1980) was an inactivated whole bacterium product and of all the childhood vaccines this one had the most problematic safety profile. It was used because whooping cough for infants and young children has very high morbidity and mortality. One of the side effects was unexplained seizures and one of my colleagues showed that there was a factor that cause spikes in insulin which could explain this (insulin shock therapy was used to treat certain mental illnesses). A number of European countries had discontinued this vaccine and there was pressure here

in the US to do so. Our local NBC affiliate ran a weeklong expose on this which was quite inflammatory. What happened next was a tragedy. Because of concern about the side effect, vaccination rates in the UK dropped dramatically and in 1978-79 there was a major outbreak of this disease. In the early 1980s an acellular vaccine was developed with a much better safety profile though it isn't quite as immunogenic as the whole cell version. There are two points here, vaccines represent a tradeoff between taking on a certain risk (which for most vaccines is very low) in return for immunity to the pathogenic microorganism. This approach has worked for many years and is a way of achieving herd immunity at little cost. The recent rise of the anti-vaccination movement has led to sporadic outbreaks of whooping cough, measles, and chicken pox showing how fragile herd immunity is and that the percentage needed to achieve this can be very high. In the case of these childhood diseases, even a drop in immunization by 10% can trigger outbreaks. There is no evidence that the herd immunity level for SARS-CoV-2 is as high as this value and I have linked to a number of papers that predict a range between 25-75%. As to what is the correct number, your guess is as good as mine. There have been some op-ed articles over the past several days objecting to The Great Barrington declaration on herd immunity as an approach that will bring needless suffering to this country. There is a lot of uncertainty of what the mortality might be if the US did nothing and let the virus run its course. My own personal thinking is that the mortality rate for COVID-19 will end up being between 0.3-0.6% of those infected. This makes it slightly worse than the 1957-58 Asian flu outbreak for which there are pretty good numbers. You can easily calculate what the mortality might be in the US if nothing is done. The equation is as follows: 330 million (population of the US) * Herd Immunity Value * Mortality Value = mortality. My thinking is the herd immunity may be 50% and with the mortality rate at the low end of the scale, this means close to 500,000 deaths from the pandemic. I don't mean this to be alarmist but to point out that this is serious albeit with lots of unknowns. Other countries are having success using the simple public health measures as outlined in my daily signature sign off. This is what we have to do and with that, **I send you back to our regularly scheduled newsletter**!!!

Speaking of vaccines, Sara Zhang has a nice article in The Atlantic on what really matters in the data. (BTW, she is wrong about the size of vaccine trials by an order of magnitude.) Alex Gibney, a fine documentary film maker, has a COVID-19 film coming out today and it's streaming on Hulu.

STAT covers the increase in new COVID-19 cases and the impact on hospitals. The FDA Vaccines Advisory Committee meets this Thursday. Here are the supporting materials for the meeting and if you scroll up a bit you can find instructions for watching a live stream of the meeting!

The Lancet have correspondence from researchers who urge caution about using a recombinant adenovirus type-5 vector for a COVID-19 vaccine. They used a similar vector for an HIV vaccine over a decade ago and observed some troubling adverse events. To my knowledge only a Chinese vaccine has been constructed with this vector. Here is a report on the estimation of infection-fatality risk in New York City from the Spring pandemic. "*Our estimated infection-fatality risk for the two oldest age groups (65–74 and ≥75 years) was much higher than the younger age groups, with a cumulative estimated infection-fatality risk of 0·116% (0·0729–0·148) for those aged 25–44 years and 0·939% (0·729–1·19) for those aged 45–64 years versus 4·87% (3·37–6·89) for those aged 65–74 years and 14·2% (10·2–18·1) for those aged 75 years and older. In particular, weekly infection-fatality risk was estimated to be as high as 6·72% (5·52–8·01) for those aged 65–74 years and 19·1% (14·7–21·9) for those aged 75 years and older*." Here is an editorial on contact tracing.

MODELING

- SARS-CoV-2 emerged in late 2019 and caused a pandemic, whereas the closely related SARS-CoV was contained rapidly in 2003. Here, a newly developed experimental set-up was used to study transmission of SARS-CoV and SARS-CoV-2 through the air between ferrets over more than a meter distance. Both viruses caused a robust productive respiratory tract infection resulting in transmission of SARS-CoV-2 to two of four indirect recipient ferrets and SARS-CoV to all four. A control pandemic A/H1N1 influenza virus also transmitted efficiently. Serological assays confirmed all virus transmission events. Although the experiments did not discriminate between transmission via small aerosols, large droplets and fomites, these results demonstrate that SARS-CoV and SARS-CoV-2 can remain infectious while traveling through the air. Efficient virus transmission between ferrets is in agreement with frequent SARS-CoV-2 outbreaks in mink farms. Although the evidence for airborne virus transmission between humans under natural conditions is absent or weak for SARS-CoV and SARS-CoV-2, ferrets may represent a sensitive model to study interventions aimed at preventing virus transmission. [**note: from Holland here is a study on aerosol transmission between ferrets that might be a sensitive model for studying the virus and interventions.**]
  https://www.biorxiv.org/content/10.1101/2020.10.19.345363v1
- A two-parameter, human behavior Covid-19 infection growth model predicts total infections between -4.2% (overprediction) and 4.5% (underprediction) of actual infections from July 27, 2020 to September 30, 2020 for 10 US States (NY, WA, GA, IL, MN, FL, OH, MI, CA, NC). During that time, total Covid-19 infections for 9 of the 10 modeled US States grew by 60% (MI) to 95% (MN). Only NY limited Covid-19 infection growth with an 11% increase from July 27 to September 30, 2020. September is a month with contraposing effects of increased social interaction (eg, physical school openings) and outdoor temperatures decreasing to the 50F (10C) to 70F (21C) range in which outdoor activities and building ventilation are beneficially increased. All State infection predictions except GA, FL and CA predictions through September 30 are bounded by four prediction scenarios (no school with outdoor temperature effect, no school with no outdoor temperature effect, school with temperature effect, school with no temperature effect). GA, FL and CA continued along a path slightly below the linear infection growth boundary separating infection growth and decay, resulting in overprediction of infection growth over the two month simulation period(-3.1% for GA, -1.9% for FL, and -4.5% for CA). Three eastern States (NY, NC, and GA) are most accurately represented by models that assume no significant change in social interactions coupled with minor outdoor temperature effects. Four midwestern States (IL, MI, MN, OH) are most accurately modeled with minor outdoor temperature effects due to a delayed decrease in average outdoor temperatures in the Midwest. The remaining three States (WA, FL, and CA) are also in good agreement with the model but with differing weather condition and social interaction impacts. *Overall, model predictions continue to support the basic premise that human behavior in the US oscillates across a linear infection growth boundary that divides accelerated infection growth and decaying infection transmission*. [**note: this is from a Univ of Illinois professor who is looking at a simple two parameter model for COVID-19 spread. He has been updating this at monthly intervals based on new data. Human behavior is the focus of his study.**]
  https://www.medrxiv.org/content/10.1101/2020.10.15.20213223v1

- The COVID-19 pandemic, caused by tens of millions of SARS-CoV-2 infections world-wide, has resulted in considerable levels of mortality and morbidity. The United States has been hit particularly hard having 20 percent of the world's infections but only 4 percent of the world population. Unfortunately, significant levels of misunderstanding exist about the severity of the disease and its lethality. As COVID-19 disproportionally impacts elderly populations, the false impression that the impact on society of these deaths is minimal may be conveyed by some because elderly individuals are closer to a natural death. To assess the impact of COVID-19 in the US, I have performed calculations of person-years of life lost as a result of 194,000 premature deaths due to SARS-CoV-2 infection as of early October, 2020. By combining actuarial data on life expectancy and the distribution of COVID-19 associated deaths we estimate that over 2,500,000 person-years of life have been lost so far in the pandemic in the US alone, averaging over 13.25 years per person with differences noted between males and females. Importantly, nearly half of the potential years of life lost occur in non-elderly populations. Issues impacting refinement of these models and the additional morbidity caused by COVID-19 beyond lethality are discussed. [**note: this is from a Harvard professor who calculates the person-years of life that have been lost because of COVID-19 in the US.**]
  https://www.medrxiv.org/content/10.1101/2020.10.18.20214783v1

NEWLY REGISTERED CLINICAL TRIALS

- It is not Wednesday yet!

CLINICAL TRIAL RESULTS

- Immune responses to respiratory viruses like SARS-CoV-2 originate and function in the lung, yet assessments of human immunity are often limited to blood. Here, we conducted longitudinal, high-dimensional profiling of paired airway and blood samples from patients with severe COVID-19, revealing immune processes in the respiratory tract linked to disease pathogenesis. Survival from severe disease was associated with increased CD4+T cells and decreased monocyte/macrophage frequencies in the airway, but not in blood. Airway T cells and macrophages exhibited tissue-resident phenotypes and activation signatures, including high level expression and secretion of monocyte chemoattractants CCL2 and CCL3 by airway macrophages. By contrast, monocytes in blood expressed the CCL2-receptor CCR2 and aberrant CD163+ and immature phenotypes. Extensive accumulation of CD163+monocyte/macrophages within alveolar spaces in COVID-19 lung autopsies suggested recruitment from circulation. *Our findings provide evidence that COVID-19 pathogenesis is driven by respiratory immunity, and rationale for site-specific treatment and prevention strategies.* [**note: this is from Columbia Univ and looks at respiratory and systemic immune response in COVID-19. It appears that there are differential responses in the blood and the airway that may lead to further treatment refinements.**] https://www.medrxiv.org/content/10.1101/2020.10.15.20208041v1

DRUG DEVELOPMENT

- The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has developed into an unprecedented global pandemic. Nucleoside analogues, such as Remdesivir and Favipiravir, can serve as the first-line broad-spectrum antiviral drugs against the newly emerging viral diseases. Recent clinical trials of these two drugs for SARS-CoV-2 treatment revealed

antiviral efficacies as well as side effects with different extents. As a pyrazine derivative, Favipiravir could be incorporated into the viral RNA products by mimicking both adenine and guanine nucleotides, which may further lead to mutations in progeny RNA copies due to the non-conserved base-pairing capacity. Here, we determined the cryo-EM structure of Favipiravir bound to the replicating polymerase complex of SARS-CoV-2 in the pre-catalytic state. This structure provides a missing snapshot for visualizing the catalysis dynamics of coronavirus polymerase, and reveals an unexpected base-pairing pattern between Favipiravir and pyrimidine residues which may explain its capacity for mimicking both adenine and guanine nucleotides. These findings shed lights on the mechanism of coronavirus polymerase catalysis and provide a rational basis for developing antiviral drugs to combat the SARS-CoV-2 pandemic. [**note; here is a model how the antiviral drug favipiravir inhibits the viral polymerase. There are a number of clinical trials but I have not seen any published results. This drug is teratogenic which may mean it doesn't get broad use if it works out.**]
https://www.biorxiv.org/content/10.1101/2020.10.19.345470v1

- The ongoing Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) pandemic has acutely highlighted the need to identify new treatment strategies for viral infections. Here we present a pivotal molecular mechanism of viral protein translation that relies on the mitochondrial translation machinery. *We found that rare codons such as Leu-TTA are highly enriched in many viruses, including SARS-CoV-2, and these codons are essential for the regulation of viral protein expression. SARS-CoV-2 controls the translation of its spike gene by hijacking host mitochondria through 5' leader and 3'UTR sequences that contain mitochondrial localization signals and activate the EGR1 pathway. Mitochondrial-targeted drugs such as lonidamine and polydatin significantly repress rare codon-driven gene expression and viral replication. This study identifies an unreported viral protein translation mechanism and opens up a novel avenue for developing antiviral drugs*. [**note: this is an interesting study that may lead to some new therapeutic approaches. The second compound also called piceid, is a resveratrol derivative and that compound has already been identified as a potential inhibitor of the virus.**] https://www.biorxiv.org/content/10.1101/2020.10.19.344713v1
- In the current global emergency due to SARS-CoV-2 outbreak, passive immunotherapy emerges as a promising treatment for COVID-19. Among animal-derived products, equine formulations are still the cornerstone therapy for treating envenomations due to animal bites and stings. Therefore, drawing upon decades of experience in manufacturing snake antivenom, we developed and preclinically evaluated two anti-SARS-CoV-2 polyclonal equine formulations as potential alternative therapy for COVID-19. We immunized two groups of horses with either S1 (anti-S1) or a mixture of S1, N, and SEM mosaic (anti-Mix) viral recombinant proteins. Horses reached a maximum anti-viral antibody level at 7 weeks following priming, and showed no major adverse acute or chronic clinical alterations. Two whole-IgG formulations were prepared via hyperimmune plasma precipitation with caprylic acid and then formulated for parenteral use. Both preparations had similar physicochemical and microbiological quality and showed ELISA immunoreactivity towards S1 protein and the receptor binding domain (RBD). The anti-Mix formulation also presented immunoreactivity against N protein. *Due to high anti-S1 and anti-RBD antibody content, final products exhibited high in vitro neutralizing capacity of SARS-CoV-2 infection, 80 times higher than a pool of human convalescent plasma. Pre-clinical quality profiles were similar among both products, but clinical efficacy and safety must be tested in*

clinical trials. The technological strategy we describe here can be adapted by other producers, particularly in low- and middle-income countries. [**note: this one is from Costa Rica and I think the first one from that country so a big shout out to them for taking the 'old time' approach by generating antibodies to SARS-CoV-2 in horses. They get good neutralizing activity but there is a problem with the species difference but it's worth a try.**]
https://www.biorxiv.org/content/10.1101/2020.10.17.343863v1

- The spike S of SARS-CoV-2 recognizes ACE2 on the host cell membrane to initiate entry. Soluble decoy receptors, in which the ACE2 ectodomain is engineered to block S with high affinity, potently neutralize infection and, due to close similarity with the natural receptor, hold out the promise of being broadly active against virus variants without opportunity for escape. Here, we directly test this hypothesis. We find an engineered decoy receptor, $sACE2_2$.v2.4, tightly binds S of SARS-associated viruses from humans and bats, despite the ACE2-binding surface being a region of high diversity. *Saturation mutagenesis of the receptor-binding domain followed by in vitro selection, with wild type ACE2 and the engineered decoy competing for binding sites, failed to find S mutants that discriminate in favor of the wild type receptor. We conclude that resistance to engineered decoys will be rare and that decoys may be active against future outbreaks of SARS-associated betacoronaviruses*. [**note: here is another approach to created a decoy receptor that binds SARS-CoV-2.**]
https://www.biorxiv.org/content/10.1101/2020.10.18.344622v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Precision epidemiology using genomic technologies allows for a more targeted approach to COVID-19 control and treatment at individual and population level, and is the urgent need of the day. It enables identification of patients who may be at higher risk than others to COVID-19-related mortality, due to their genetic architecture, or who might respond better to a COVID-19 treatment. The COVID-19 virus, similar to SARS-CoV, uses the ACE2 receptor for cell entry and employs the cellular serine protease TMPRSS2 for viral S protein priming. This study aspires to present a multi-omics view of how variations in the ACE2 and TMPRSS2 genes affect COVID-19 infection and disease progression in affected individuals. It reports, for both genes, several variant and gene expression analysis findings, through (i) comparison analysis over single nucleotide polymorphisms (SNPs), that may account for the difference of COVID-19 manifestations among global sub-populations; (ii) calculating prevalence of structural variations (copy number variations (CNVs) / insertions), amongst populations; and (iii) studying expression patterns stratified by gender and age, over all human tissues. This work is a good first step to be followed by additional studies and functional assays towards informed treatment decisions and improved control of the infection rate. [**note: this is an interesting paper from Taiwan that looks at multi-omics view of variations in genes can impact COVID-19 progression. We need more of this work to zero in on the key factors and how to address them.**]
https://www.biorxiv.org/content/10.1101/2020.10.19.345140v1
- While the current pandemic remains a thread to human health, the polyclonal nature of the antibody response against SARS-CoV-2 is not fully understood. Other than SARS-CoV-2, humans are susceptible to six different coronaviruses, and previous exposure to antigenically related and divergent seasonal coronaviruses is frequent. We longitudinally profiled the early humoral immune response against SARS-CoV-2 on hospitalized COVID-19 patients, and quantify levels of

pre-existing immunity to OC43, HKU1 and 223E seasonal coronaviruses. A strong back-boosting effect to conserved, but not variable regions of OC43 and HKU1 betacoronaviruses spike protein was observed. All patients developed antibodies against SARS-CoV-2 spike and nucleoprotein, with peak induction at day 7 post hospitalization. *However a negative correlation was found between antibody memory boost to human coronaviruses and induction of IgG and IgM against SARS-CoV-2 spike. Our findings provide evidence of immunological imprinting that determine the antibody profile to COVID-19 patients in an original antigenic sin fashion*. [**note: more work from the Mt. Sinai group. They looks at the impact of pre-existing immunity to seasonal coronaviruses. This is a complicated paper for the non-immunologist (me) and may have an impact on the Spike vaccine performance.**]
https://www.medrxiv.org/content/10.1101/2020.10.14.20212662v1

DIAGNOSTIC DEVELOPMENT

- Here we describe COVID-19 screening using Systematic Parallel Analysis of RNA coupled to Sequencing (C19-SPAR-Seq), a scalable, multiplexed, readily automated next generation sequencing (NGS) platform that is capable of analyzing tens of thousands of COVID-19 patient samples in a single instrument run. To address the strict requirements in clinical diagnostics for control of assay parameters and output, we employed a control-based Precision-Recall and predictive Receiver Operator Characteristics (coPR) analysis to assign run-specific quality control metrics. C19-SPAR-Seq coupled to coPR on a trial cohort of over 600 patients performed with a specificity of 100% and sensitivity of 91% on samples with low viral loads and a sensitivity of > 95% on high viral loads associated with disease onset and peak transmissibility. Our study thus establishes the feasibility of employing C19-SPAR-Seq for the large-scale monitoring of SARS-CoV-2 and other pathogens. [**note: this is from a Toronto research group and discusses a new platform for large scale monitoring of SARS-CoV-2.**]
https://www.medrxiv.org/content/10.1101/2020.10.15.20212712v1

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2020-10-21

He's only 94 years old, but Tony Bennett can still shape a song. Here he is from home in a pandemic rendition of 'The Way You Look Tonight': https://www.youtube.com/watch?v=vq3z9HlDlec I don't have anything to add.

The Washington Post reports on a CDC report that the pandemic has caused nearly 300K more deaths than expected in a typical year. Despite knowing what to do every resident in the Kansas nursing home was infected with COVID-19; ten have died. I'm waiting to hear from The Great Barrington people about this one! Sweden have imposed first localized restrictions as case have increased. Will we have standards for COVID-19 masks? Enquiring minds want to know. I'm reminded of the great Frank Zappa song 'Montana' that I linked to some months ago when I read this article of people moving to that state. A large wedding in Mexico turns into a superspreader event; when will people learn? Hospital bed utilization in New Mexico reaches 81%.

JAMA have multicenter cohort study of almost 4000 patients that shows lower in hospital death if tocilizumab is administered within the first two days of ICU admission……but……there is also a paper from Italy on a RCT for treatment of COVID-19 pneumonia that shows no effect of the drug…and….there is this Italian paper that shows tocilizumab may reduce the need for mechanical and noninvasive ventilation or death by day 14 but not mortality by day 28; further studies are necessary to confirm these preliminary results…..and…..this editorial tries to make sense of it all. This article discusses some key questions about COVID-19 vaccines (the principal author is the former head of the FDA Center that regulates vaccines). The New York Times is reporting on a CDC study showing COVID-19 outcomes worse than severe flu. CDC study is HERE. This Montana school district is moving students around every 15 minutes; maybe it will work! Here is the clip on the Kansas nursing home. It looks like the US is into the third wave of COVID-19. This was pretty much predicted by the early CIDRAP paper that outlined several different wave scenarios. The FDA is pushing back against the Administration regarding early vaccine availability. Monoclonal antibody treatments will initially be in short supply as manufacturing begins to ramp up. Here is the story of a young physician who has had lingering COVID-19 after effects. Here is good commentary on post approval vaccine safety surveillance for COVID-19 vaccines and another one discussing how vaccines should be evaluated once approved.

From my Yahoo news feed: how cool would it be if this 14 year-old girl unlocked the cure for COVID-19? Way cool!!!

STAT discusses how dry indoor air will help spread COVID-19. This is not a surprise as the same phenomenon is seen with seasonal influenza.

The Lancet has a commentary on a life-course model for healthier aging and the lessons learned during the pandemic.

Nature have a good overview of the state of the vaccine race. This article goes into the specific vaccines in development. It is a very nice albeit technical paper on the topic.

Kaiser Health News has a story about one patient who enrolls in a Regeneron mAb trial.

MODELING

- ABSTRACT Despite the high level of morbidity and mortality worldwide, there is increasing evidence for asymptomatic carriers of the novel coronavirus SARS-CoV-2. *We analyzed blood specimens from 1,559 healthy blood donors, collected in the greater New York metropolitan area between the months of March and July 2020 for antibodies to SARS-CoV-2 virus. Using our proprietary technology, SERA (Serum Epitope Repertoire Analysis), we observed a significant increase in SARS-CoV-2 seropositivity rates over the four-month period, from 0% [95% CI: 0 - 1.5%] (March) to 11.6% [6.0 - 21.2%] (July). Follow-up ELISA tests using S1 and nucleocapsid viral proteins confirmed most of these results*. Our findings are consistent with seroprevalence studies within the region and with reports that SARS-COV-2 infections can be asymptomatic or cause only mild symptoms. IMPORTANCE The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has caused vast morbidity and mortality worldwide, yet several studies indicate that there may be a significant number of infected people who are asymptomatic or exhibit mild symptoms. In this study, samples were collected from healthy blood donors in a

region of rapidly increasing disease burden (New York metropolitan area) and we hypothesized that a subset would be seropositive to SARS-CoV-2. People who experienced mild or no symptoms during SARS-CoV-2 infection may represent a source for convalescent plasma donors. [**note: here is a seroprevalence study of health blood donors in New York.]** https://www.medrxiv.org/content/10.1101/2020.10.19.20215368v1

NEWLY REGISTERED CLINICAL TRIALS

- This is a phase 1b, open-label study in adult healthy subjects. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of the hAd5-S-Fusion+N-ETSD vaccine and select a dose for future studies. [**note: here is a vaccine trial from a company I've not heard of, ImmunityBio. It is an adenovirus vector that delivers both Spike and Nucleocapsid antigens.]** NCT04591717
- ACTIV-1 IM is a master protocol designed to evaluate multiple investigational agents for the treatment of moderately or severely ill patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The research objectives are to evaluate each agent with respect to speed of recovery, mortality, illness severity, and hospital resource utilization. Each agent will be evaluated as add-on therapy to the standard of care (SoC) in use at the local clinics, including remdesivir (provided). The SoC may change during the course of the study based on other research findings. Comparisons of the agents among themselves is not a research objective. [**note: this is a trial at Duke and will look at infliximab, abatacept, and cenicriviroc in addition to remdesivir.**] NCT04593940
- Efficacy and safety of Drug combination therapy of Isotretinoin and some Anti fungal Drugs as A potential Aerosol therapy for COVID-19 : An innovative therapeutic approach [**note: this is an Egyptian trial and you will need to look it up to read the full abstract as it's somewhat complicated.**] NCT04577378
- Virgin Coconut Oil (VCO) contains multiple compounds which have antibacterial, antiviral, and immunomodulatory properties. The role of VCO as an antivirus to treat COVID-19 requires further studies. A previous study has investigated the used of 30 ml of VCO to healthy volunteers for a month and reported no side effect. Here the investigators conduct a pilot trial to investigate the effect of VCO towards the clinical outcomes of COVID-19 patients in Indonesia. [**note: unlikely that this will work but shout out to these Indonesian researchers for giving it a try!!!**] NCT04594330

CLINICAL TRIAL RESULTS

- Case studies have revealed neurological problems in severely affected COVID-19 patients. However, there is little information regarding the nature and broader prevalence of cognitive problems post-infection or across the full spread of severity. We analysed cognitive test data from 84,285 Great British Intelligence Test participants who completed a questionnaire regarding suspected and biologically confirmed COVID-19 infection. *People who had recovered, including those no longer reporting symptoms, exhibited significant cognitive deficits when controlling for age, gender, education level, income, racial-ethnic group and pre-existing medical disorders. They were of substantial effect size for people who had been hospitalised, but also for mild but biologically confirmed cases who reported no breathing difficulty. Finer grained analyses of performance support the hypothesis that COVID-19 has a multi-system impact on*

human cognition. [**note: this is from the UK. I'm not a fan of these kinds of studies but they can be useful for generating some finer grained ones.**]
https://www.medrxiv.org/content/10.1101/2020.10.20.20215863v1

- The recent studies suggest that anti-cytokine targeted therapies might be associated with benefit for patients with severe COVID-19 especially in improving respiratory failure. Tocilizumab, a monoclonal antibody against interleukin 6 (IL6) receptor, is associated with clinical benefit for COVID-19 patients as it inhibits IL6 and decreases inflammation. Methods: As Tocilizumab has been an important part of our treatment and a strict criterion was followed to administer Tocilizumab, a retrospective study design used to assess the beneficial effects of Tocilizumab in improvement of ratio partial pressure of arterial Oxygen and fraction of inspired Oxygen (PaO2/FiO2 or P/F ratio) and C- reactive protein (CRP) in COVID19 patients has been done. 60 patients were taken for this study by using convenient sampling technique the data of demographics, laboratory results, and clinical outcomes i.e. improvement of respiratory failure depicted in the form of PF Ratio were obtained from the medical records, Statistical analysis was done with SPSS, version 21.0. Results: Sixty patients (47 males and 13 females) with COVID-19 were included in this study, the mean age of patients was 53.83 (14-81) years. After administration of Tocilizumab the lab parameters were changed as CRP decreased down to .40 (9.6-73) mg/L but other parameters were not affected. The PF ratio improved in COVID-19 patients after administration of Tocilizumab the median of PF Ratio before treatment was 108 (52-362) and improved up to 128 (37-406) after Tocilizumab therapy. Conclusion: *In summary, Tocilizumab appears to be associated with improvement in P/F Ratio and CRP in COVID19 patients but other markers did not improve in response to Tocilizumab therapy in severely ill COVID-19 patients*. [**note: here is a tocilizumab study from Pakistan that shows a modes treatment effect on two markers of COVID-19**]
https://www.medrxiv.org/content/10.1101/2020.10.20.20210195v1
- We compared symptoms and characteristics of 4961 ambulatory patients with and without laboratory-confirmed SARS-CoV-2 infection. Findings indicate that clinical symptoms alone would be insufficient to distinguish between COVID-19 and other respiratory infections (e.g., influenza) and/or to evaluate the effects of preventive interventions (e.g., vaccinations). [**note: this is from CDC and several medical centers. Clinical symptoms alone cannot define whether a patient has COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.10.20.20213272v1
- Reports of "Long-COVID", are rising but little is known about prevalence, risk factors, or whether it is possible to predict a protracted course early in the disease. We analysed data from 4182 incident cases of COVID-19 who logged their symptoms prospectively in the COVID Symptom Study app. 558 (13.3%) had symptoms lasting >28 days, 189 (4.5%) for >8 weeks and 95 (2.3%) for >12 weeks. *Long-COVID was characterised by symptoms of fatigue, headache, dyspnoea and anosmia and was more likely with increasing age, BMI and female sex. Experiencing more than five symptoms during the first week of illness was associated with Long-COVID, OR=3.53 [2.76;4.50]. Our model to predict long-COVID at 7 days, which gained a ROC-AUC of 76%, was replicated in an independent sample of 2472 antibody positive individuals. This model could be used to identify individuals for clinical trials to reduce long-term symptoms and target education and rehabilitation services*. [**note: this is the first study I've seen that looks at predictive parameters for 'long-haul' syndrome. The sex link issue is interesting given that men seem to suffer greater mortality.**] https://www.medrxiv.org/content/10.1101/2020.10.19.20214494v1

- Background The efficacy of hydroxychloroquine in coronavirus disease 2019 (COVID-19) remains controversial. Methods We conducted a multicentre randomized double-blind placebo-controlled trial evaluating hydroxychloroquine in COVID-19 patients with at least one of the following risk factors for worsening: age 75 years or more, age between 60 and 74 years, and presence of at least one comorbidity, or need for supplemental oxygen (3 L/min or more). Eligible patients were randomized in a 1:1 ratio to receive either 800 mg hydroxychloroquine on Day 0 followed by 400 mg per day for 8 days or a placebo. The primary endpoint was a composite of death or tracheal intubation within 14 days following randomization. Secondary endpoints included mortality and clinical evolution at Day 14 and 28, viral shedding at Day 5 and 10. Results The trial was stopped after 250 patients were included due to a slowdown of the pandemic in France. The intention-to-treat population comprised 123 and 124 patients in the placebo and hydroxychloroquine groups, respectively. The median age was 77 years and 151 patients required oxygen therapy. The primary endpoint occurred in nine patients in the hydroxychloroquine group and eight patients in the placebo group (relative risk 1.12; 95% confidence interval 0.45-2.80; P=0.82). *No difference was observed between the two groups in any of the secondary endpoints. Conclusion In this trial involving mainly older patients with mild-to-moderate COVID-19, patients treated with hydroxychloroquine did not experience better clinical or virological outcomes than those receiving the placebo*. [**note: another wooden stake to the heart of HCQ therapy.**]
  https://www.medrxiv.org/content/10.1101/2020.10.19.20214940v1

DRUG DEVELOPMENT

- Establishing new experimental animal models to assess the safety and immune response to the antigen used in the development of COVID-19 vaccine is an imperative issue. Based on the advantages of using zebrafish as a model in research, herein we suggest doing this to test the safety of the putative vaccine candidates and to study immune response against the virus. We produced a recombinant N-terminal fraction of the Spike SARS-CoV-2 protein and injected it into adult female zebrafish. The specimens generated humoral immunity and passed the antibodies to the eggs. However, they presented adverse reactions and inflammatory responses similar to severe cases of human COVID-19. The analysis of the structure and function of zebrafish and human Angiotensin-converting enzyme 2, the main human receptor for virus infection, presented remarkable sequence similarities. Moreover, bioinformatic analysis predicted protein-protein interaction of the Spike SARS-CoV-2 fragment and the Toll-like receptor pathway. It might help in the choice of future therapeutic pharmaceutical drugs to be studied. Based on the in vivo and in silico results presented here, we propose the zebrafish as a model for translational research into the safety of the vaccine and the immune response of the vertebrate organism to the SARS-CoV-2 virus. [**note: these Brazilian researchers propose that the zebrafish be looked at as an animal model for vaccine safety and immune response. I didn't even know about the zebrafish until reading this. This newsletter is full of wonderful stuff!**] https://www.biorxiv.org/content/10.1101/2020.10.20.346262v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- The SARS-CoV-2 virus is the cause of the ongoing coronavirus disease 2019 (COVID-19) pandemic, infecting millions of people and causing more than a million deaths. The SARS-CoV-2

Spike glycoproteins mediate viral entry and represent the main target for antibody responses. Humoral responses were shown to be important for preventing and controlling infection by coronaviruses. A promising approach to reduce the severity of COVID-19 is the transfusion of convalescent plasma. However, longitudinal studies revealed that the level of antibodies targeting the receptor-binding domain (RBD) of the SARS-CoV-2 Spike declines rapidly after the resolution of the infection. Study Design and Methods: To extend this observation beyond the RBD domain, we performed a longitudinal analysis of the persistence of antibodies targeting the full-length SARS-CoV-2 Spike in the plasma from 15 convalescent donors. We generated a 293T cell line constitutively expressing the SARS-CoV-2 Spike and used it to develop a high-throughput flow cytometry-based assay to detect SARS-CoV-2 Spike specific antibodies in the plasma of convalescent donors. Results and Conclusion: *We found that the level of antibodies targeting the full-length SARS-CoV-2 Spike declines gradually after the resolution of the infection. This decline was not related to the number of donations, but strongly correlated with the decline of RBD-specific antibodies and the number of days post-symptom onset. These findings help to better understand the decline of humoral responses against the SARS-CoV-2 Spike and provide important information on when to collect plasma after recovery from active infection for convalescent plasma transfusion*. [**note: here is a Montreal study of antibodies against the Spike protein from convalescent patients.]**
https://www.biorxiv.org/content/10.1101/2020.10.20.346783v1

- The coronavirus spike glycoprotein, located on the virion surface, is the key mediator of cell entry. As such, it is an attractive target for the development of protective antibodies and vaccines. Here we describe two human monoclonal antibodies, 1.6C7 and 28D9, that display a remarkable cross-reactivity against distinct species from three Betacoronavirus subgenera, capable of binding the spike proteins of SARS-CoV and SARS-CoV-2, MERS-CoV and the endemic human coronavirus HCoV-OC43. Both antibodies, derived from immunized transgenic mice carrying a human immunoglobulin repertoire, blocked MERS-CoV infection in cells, whereas 28D9 also showed weak cross-neutralizing potential against HCoV-OC43, SARS-CoV and SARS-CoV-2 in a neutralization-sensitive virus pseudotyping system, but not against authentic virus. Both cross-reactive monoclonal antibodies were found to target the stem helix in the spike protein S2 fusion subunit which, in the prefusion conformation of trimeric spike, forms a surface exposed membrane-proximal helical bundle, that is antibody-accessible. We demonstrate that administration of these antibodies in mice protects from a lethal MERS-CoV challenge in both prophylactic and/or therapeutic models. Collectively, these antibodies delineate a conserved, immunogenic and vulnerabe site on the spike protein which spurs the development of broad-range diagnostic, preventive and therapeutic measures against coronaviruses. [**note: this is a Dutch study on the cross reactivity of two monoclonal antibody against divergent coronaviruses that shows the conserved vulnerable site on the Spike protein.**]
https://www.biorxiv.org/content/10.1101/2020.10.20.346916v1

DIAGNOSTIC DEVELOPMENT

- Objectives: This study was primarily conducted to evaluate clinical sensitivity and specificity of the SARS-CoV-2 rapid antigen test BD Veritor System for Rapid Detection of SARS-CoV-2 (VRD) compared to real time reverse transcriptase polymerase chain reaction (qRT-PCR). Furthermore, the VRD sensitivity for different Ct-value groups (Ct <20; Ct 20-25, Ct 25-30 and Ct > 30) and

different intervals since symptom onset (< 7 days; > 7 days) were examined. Design: Prospective performance evaluation study. Setting: Municipal Health Service (GGD) COVID-19 test centres in West-Brabant, the Netherlands Participants: In order to evaluate clinical specificity, 352 symptomatic adults (> 18 years) who presented at a participating GGD test centre for a COVID-19 test between September 28 and October 7 2020 were included. In order to evaluate clinical sensitivity, 123 symptomatic adults (> 18 years) who were tested positive with qRT-PCR in a participating GGD test centre between September 26 and October 6 were included. Results: An overall clinical specificity of 100% (95%CI : 98.9%-100%) and sensitivity of 80.7% (95% CI: 73,2%-86,9%) was found for the VRD compared to qRT-PCR. Sensitivity was the highest for low Ct-value categories and for specimen obtained within the first days after disease onset. For specimen obtained within 7 days after onset of symptoms, the overall sensitivity was 91.0% (95%: CI 82,4%-96,3%) and 98,6% (95%: CI 92,3%-100%) for samples with qRT-PCR Ct-value beneath 30. Conclusion: The VRD is a promising diagnostic test for COVID-19 community screening for symptomatic individuals within 7 days after symptom onset in function of disease control. The clinical sensitivity was highest when viral load was high, which correlated with the duration of symptoms. Further research on practical applicability and the optimal position of the test within the current testing landscape is needed. [**note: I have not been posting many of these types of studies as there are a lot of them. This one seems interesting as it is in a community setting and uses one of the newer rapid antigen tests.**]
https://www.medrxiv.org/content/10.1101/2020.10.19.20215202v1

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2020-10-22

For today music selection we have the great Andras Schiff both at the keyboard and directing this performance of Beethoven's Third Piano Concerto: https://www.youtube.com/watch?v=FnN9GEpyREQ the orchestra is the Cappella Andrea Barca which for those of you smarties who know Italian will recognize that it is named after the conductor! Here is the soloists/conductor with the group in the Beethoven Piano Concerto #5 for a double Thursday delight:
https://www.youtube.com/watch?v=QEKsMz37AkY

You can call this one the 'poop scoop.' The Washington Post notes that scientists around the world are turning to sewage sampling to monitor SARS-CoV-2 outbreaks. This should come as no surprise to my readers as I have been writing on this topic for several months. Here's an article on the FDA Vaccine Advisory Committee meeting that is taking place today. CDC has expanded the definition of who is a 'close contact' of an infected individual. Wearing a mask significantly can reduce a 'cough cloud.' As Homer Simpson would say, "doh." Things did not turn out well when college students returned to LaCrosse Wisconsin. When will they ever learn? Wearing masks should be mandatory. If you cannot do contact tracing at the government level, ask the citizens to do it themselves. Do you think this will work? I don't. Here is a story on hotel ventilation systems. Chris Christie laments not paying attention to prudent public health measures.

The New York Times has an op-ed arguing to pay bars and restaurants to close down because of the pandemic. This makes sense as they have the potential to be superspreader sites. Here is a story on

whether mouthwashes are really good antiviral treatments. Even young girls can suffer from COVID-19 long-haul symptoms.

STAT have a story about Operation Warp Speed director Moncef Slaoui and whether he should be dismissed. This is too stupid and I will make an **editorial comment:** he has addressed all the relevant conflicts of interest and his expertise in vaccine development is needed. Get politics out of this particular issue!

JAMA have a news piece on the challenge of expanding rapid COVID-19 testing. Here is an interesting piece on the utility of college COVID-19 dashboards. There is a link to the site where they evaluate them (Mitch Daniels can be proud that Purdue University earned an 'A').

The New England Journal of Medicine has a research paper on the efficacy of tocilizumab in hospitalized patients. More confounding results on this drug as they find, "Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide." Here is a piece on the use of testing in school reopenings.

Not many new papers today.

MODELING

- Widespread school closures occurred during the COVID-19 pandemic. Because closures are costly and damaging, many jurisdictions have since reopened schools with control measures in place. Early evidence indicated that schools were low risk and children were unlikely to be very infectious, but it is becoming clear that children and youth can acquire and transmit COVID-19 in school settings and that transmission clusters and outbreaks can be large. We describe the contrasting literature on school transmission, and argue that the apparent discrepancy can be reconciled by heterogeneity, or ``overdispersion'' in transmission, with many exposures yielding little to no risk of onward transmission, but some unfortunate exposures causing sizeable onward transmission. In addition, respiratory viral loads are as high in children and youth as in adults, pre- and asymptomatic transmission occur, and the possibility of aerosol transmission has been established. We use a stochastic individual-based model to find the implications of these combined observations for cluster sizes and control measures. We consider both individual and environment/activity contributions to the transmission rate, as both are known to contribute to variability in transmission. *We find that even small heterogeneities in these contributions result in highly variable transmission cluster sizes in the classroom setting, with clusters ranging from 1 to 20 individuals in a class of 25. None of the mitigation protocols we modeled, initiated by a positive test in a symptomatic individual, are able to prevent large transmission clusters unless the transmission rate is low (in which case large clusters do not occur in any case). Among the measures we modeled, only rapid universal monitoring (for example by regular, onsite, pooled testing) accomplished this prevention. We suggest approaches and the rationale for mitigating these ``unfortunate events'', even if they are expected to be rare*. [**note: here is a piece from Simon Fraser Univ on the unfortunate events in schools regarding SARS-CoV-2 transmission.**]
https://www.medrxiv.org/content/10.1101/2020.10.20.20216267v1

NEWLY REGISTERED CLINICAL TRIALS

- I checked them yesterday.

CLINICAL TRIAL RESULTS

- Nothing new in terms of pre-prints.

DRUG DEVELOPMENT

- Translation of open reading frame 1b (ORF1b) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) requires programmed −1 ribosomal frameshifting (−1 PRF) promoted by an RNA pseudoknot. The extent to which SARS-CoV-2 replication may be sensitive to changes in −1 PRF efficiency is currently unknown. Through an unbiased, reporter-based high-throughput compound screen, we identified merafloxacin, a fluoroquinolone antibacterial, as a −1 PRF inhibitor of SARS-CoV-2. Frameshift inhibition by merafloxacin is robust to mutations within the pseudoknot region and is similarly effective on −1 PRF of other beta coronaviruses. Importantly, frameshift inhibition by merafloxacin substantially impedes SARS-CoV-2 replication in Vero E6 cells, thereby providing the proof of principle of targeting −1 PRF as an effective antiviral strategy for SARS-CoV-2. [**note: here is another paper looking at how to attack the virus through induced frameshift mutations. I've seen a couple other papers on this. I cannot find any reference that notes that this antibiotic has been approved anywhere.**] https://www.biorxiv.org/content/10.1101/2020.10.21.349225v1
- The RNA polymerase inhibitor, favipiravir, is currently in clinical trials as a treatment for infection with SARS-CoV-2, despite limited information about the molecular basis for its activity. Here we report the structure of favipiravir ribonucleoside triphosphate (favipiravir-RTP) in complex with the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) bound to a template:primer RNA duplex, determined by electron cryomicroscopy (cryoEM) to a resolution of 2.5 Ang. The structure shows clear evidence for the inhibitor at the catalytic site of the enzyme, and resolves the conformation of key side chains and ions surrounding the binding pocket. Polymerase activity assays indicate that the inhibitor is weakly incorporated into the RNA primer strand, and suppresses RNA replication in the presence of natural nucleotides. The structure reveals an unusual, non-productive binding mode of favipiravir-RTP at the catalytic site of SARS-CoV2 RdRp which explains its low rate of incorporation into the RNA primer strand. Together, these findings inform current and future efforts to develop polymerase inhibitors for SARS coronaviruses. [**note: here is another paper on the mechanism of favipiravir.]** https://www.biorxiv.org/content/10.1101/2020.10.21.347690v1
- To fight against the worldwide COVID-19 pandemic, the development of an effective and safe vaccine against SARS-CoV-2 is required. As potential pandemic vaccines, DNA or RNA vaccines, viral vector vaccines and protein-based vaccines have been rapidly developed to prevent pandemic spread worldwide. In this study, we designed plasmid DNA vaccine targeting the SARS-CoV-2 Spike glycoprotein (S protein) as pandemic vaccine, and the humoral, cellular, and functional immune responses were characterized to support proceeding to initial human clinical trials. After intramuscular injection of DNA vaccine encoding S protein with alum adjuvant (three times at 2-week intervals), the humoral immunoreaction, as assessed by anti-S protein or anti-receptor-binding domain (RBD) antibody titers, and the cellular immunoreaction, as assessed by

antigen-induced IFN-g expression, were up-regulated. In IgG subclass analysis, IgG2b was induced as the main subclass. Based on these analyses, DNA vaccine with alum adjuvant preferentially induced Th1-type T cell polarization. We confirmed the neutralizing action of DNA vaccine-induced antibodies via two different methods, a binding assay of RBD recombinant protein with angiotensin-converting enzyme 2 (ACE2), a receptor of SARS-CoV-2, and pseudovirus assay. Further B cell epitope mapping analysis using a peptide array showed that most vaccine-induced antibodies recognized the S2 and RBD subunits, but not the S1 subunit. In conclusion, DNA vaccine targeting the spike glycoprotein of SARS-CoV-2 might be an effective and safe approach to combat the COVID-19 pandemic. [**note: here is a preclinical study of a DNA vaccine from Japan. This one is a bit different in that it is on a plasmid and that is what is injected.**] https://www.biorxiv.org/content/10.1101/2020.10.21.347799v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Nothing new.

DIAGNOSTIC DEVELOPMENT

- Nothing new.

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2020-10-23

One of my favorite singers of all time is the late American soprano, Arleen Auger. Most of her fame came in Europe where she was active on the opera stage as well as recitals. Perhaps her most famous gig was singing Mozart's Exultate Jubilate at the wedding of Sarah Ferguson and Prince Andrew. Here she is singing this piece with the Bavarian Radio Orchestra conducted by Leonard Bernstein: https://www.youtube.com/watch?v=co8l3GSkbaA The performance of Richard Strauss's 'Morgen' is sublime: https://www.youtube.com/watch?v=mDfVbF1UTGc the song requires good breath control and you cannot get overly involved in the long piano introduction or you will miss coming in (I sang this several years ago in recital and almost missed the entry 😉 ; about a year later I was at a post recital dinner party and was talking with pianist Malcolm Martineau who accompanies many leading singers and I asked him whether he ever had a singer who was so entranced by his playing that he/she missed the entry; he laughed and said he wasn't that good a pianist.). Auger's last recorded performance was a Mozart Requiem with Cecilia Bartoli, Vinson Cole and Rene Pape with Georg Solti conducting: https://www.youtube.com/watch?v=zKE6rn9-xr8 and a few months later she was diagnosed with a brain tumor that ultimately took her life at the age of 53. While not a video, I must commend this version of Strauss's 'Four Last Songs': https://www.youtube.com/watch?v=JuTbILSdD14 I probably have 14 recordings of this and this is always the one that brings me pleasure. It's from 1988 with Andre Previn and the Vienna Philharmonic.

The New York Times has an interesting story of the Seattle fishing trawler that left port with 122 crew who were screened using PCR and all the tests were negative. SARS-CoV-2 still found it's way onto the boat and one crew member became seriously ill. The epidemiology of this boat is extremely interesting as the infection rate was 88%. 3 sailors had antibodies to the virus and were not infected. High school football in Texas is affected by COVID-19; the virus doesn't have boundaries. The CDC testified to Congress, noting that its guidance document on schools and childhood transmission are out of date. *Dr.*

Michael Beach, the C.D.C.'s deputy incident manager for Covid-19 response, told the subcommittee that "it does appear that children can become infected" and that children "clearly can transmit," according to the statement. California's virus levels in the population are lower than all but six states. Let's hope this continues! Reported cases of COVID-19 hit the second highest daily level since the start of the pandemic; this is not good. Cases on college campuses are also rising! As you know, I follow Purdue University and their efforts to control COVID-19. The overall positivity rate does not show any marked rise over the 2.8% they have been observing. Good work to Mitch Daniels!!! Vermont appears to be doing a good job at virus control.

The Washington Post comments on the start of the Big Ten football season. You don't have to wipe down your groceries, focus on other risks (I never worried about this, or picking up the morning papers, or the mail). Moderna's mRNA vaccine trial is fully enrolled and they may have sufficient data in November. Here is a story on the FDA Vaccines Advisory Committee that took place yesterday. It is going to be a tough call for some whether to dine inside at restaurants during the winter months. For me it's easy; just say no. FDA has given a full marketing approval for remdesivir (trade name Veklury and don't ask me how they came up with that one). Gilead can now begin charging for the drug. Here is an article that clearly shows the benefits of wearing a mask. Yes, it is crude observational data but it is persuasive. MASK UP!!! Unfortunately, this Idaho community didn't understand the value of masks. Cases among ice hockey players in New England prompts closure.

The Lancet has a news piece on the double threat of COVID-19 and influenza. Here is an article on the temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (R) of SARS-CoV-2 (whew, is that a long title!). *Individual NPIs, including school closure, workplace closure, public events ban, ban on gatherings of more than ten people, requirements to stay at home, and internal movement limits, are associated with reduced transmission of SARS-CoV-2, but the effect of introducing and lifting these NPIs is delayed by 1–3 weeks, with this delay being longer when lifting NPIs. These findings provide additional evidence that can inform policy-maker decisions on the timing of introducing and lifting different NPIs, although* R *should be interpreted in the context of its known limitations.* There is also a commentary on this noting that estimating 'R' may be a bargain with the devil.

Nature have a good article on the false promise of herd immunity. There is also an article on the proposed UK human challenge vaccine trial.

Derek Lowe talks about the current state of vaccines as the first two trials near completion.

Steve Usdin of BioCentury has a good article on what an early EUA for a vaccine means for other vaccine company clinical trials. I worry about this also, particularly if the 'best' vaccine is not the first one out of the blocks (one only need look at the development of statin drugs to know that this has a good chance of being true. Atorvastatin aka Lipitor was the fifth drug in the class to be approved and turned out to have the best benefit/risk profile).

MODELING

- PURPOSE: There has been considerable controversy regarding susceptibility of adolescents (10-19 years) and youth (15-24 years) to COVID-19. A number of studies have reported that

adolescents are significantly less susceptible than older adults. Summer 2020 provided an opportunity to examine data on prevalence since after months of lockdowns, with the easing of restrictions, people were mingling, leading to surges in cases. METHODS: We examined data from six U.S. states experiencing surges in the number of cases to determine prevalence of COVID-19, and two other measures, related to prevalence in adolescents and youth as compared to older adults. The two other measures were: Percentage of cases observed in a given age group ÷ by the percentage of cases expected based on population demographics; and percentage deviation, or [(% observed− % expected)÷ % expected] ×100. RESULTS: Prevalence of COVID-19 for adolescents and for youth was significantly greater than for older adults ($p<.00001$), as was percentage observed ÷ percentage expected ($p<.005$). The percentage deviation was significantly greater in adolescents/youth than in older adults ($p<0.00001$) when there was an excess of observed cases over what was expected, and significantly less when observed cases were fewer than expected ($p<0.00001$). CONCLUSIONS: Our results are contrary to previous findings that adolescents are less susceptible than older adults. The findings have implications for school re-openings. The age groups 10-19 and 15-24 are students in middle school, high school, college, and the first two years of professional/graduate school. The high prevalence in these age groups would argue against school re-openings in the near future. [**note: YIKES! Maybe we should not be opening schools where there are viral surges in the population.**] https://www.medrxiv.org/content/10.1101/2020.10.20.20215541v1

- New Zealand responded to the COVID-19 pandemic with a combination of border restrictions and an Alert Level system that included strict stay-at-home orders. These interventions were successful in containing the outbreak and ultimately eliminating community transmission of COVID-19. The timing of interventions is crucial to their success. Delaying interventions for too long may both reduce their effectiveness and mean that they need to be maintained for a longer period of time. Here, we use a stochastic branching process model of COVID-19 transmission and control to simulate the epidemic trajectory in New Zealand and the effect of its interventions during its COVID-19 outbreak in March-April 2020. We use the model to calculate key outcomes, including the peak load on the contact tracing system, the total number of reported COVID-19 cases and deaths, and the probability of elimination within a specified time frame. We investigate the sensitivity of these outcomes to variations in the timing of the interventions. We find that a delay to the introduction of Alert Level 4 controls results in considerably worse outcomes. Changes in the timing of border measures have a smaller effect. We conclude that the rapid response in introducing stay-at-home orders was crucial in reducing the number of cases and deaths and increasing the probability of elimination. [**note: this is from a New Zealand group that discusses the country's approach to controlling the COVID-19 pandemic. I'll restrain myself from making a sarcastic political comment but you all know what I am thinking.**😱] https://www.medrxiv.org/content/10.1101/2020.10.20.20216457v1
- Background: During New Zealand's first outbreak in early 2020 the Southern Region had the highest per capita SARS-CoV-2 infection rate. PCR testing was initially limited by a narrow case definition and limited laboratory capacity, so cases may have been missed. Objectives: To evaluate the Abbott SARS-CoV-2 IgG nucleocapsid assay, alongside spike-based assays, and to determine the frequency of antibodies among PCR-confirmed and probable cases, contacts, and higher risk individuals in the Southern Region of NZ. Study design: Pre-pandemic sera (n=300) were used to establish assay specificity and sera from PCR-confirmed SARS-CoV-2 patients

(n=78) to establish sensitivity. For prevalence analysis, all samples (n=1214) were tested on the Abbott assay, and all PCR-confirmed cases (n=78), probable cases (n=9), and higher risk individuals with grey-zone (n=14) or positive results (n=11) were tested on four additional SARS-CoV-2 serological assays. Results: The median time from infection onset to serum collection for PCR-confirmed cases was 14 weeks (range 11-17 weeks). The Abbott assay demonstrated a specificity of 99.7% (95% CI, 98.2%-99.99%) and a sensitivity of 76.9% (95% CI, 66.0%-85.7%). Spike-based assays demonstrated superior sensitivity ranging 89.7-94.9%. Nine previously undiagnosed sero-positive individuals were identified, and all had epidemiological risk factors. Conclusions: Spike-based assays demonstrated higher sensitivity than the Abbott IgG assay, likely due to temporal differences in antibody persistence. No unexpected SARS-CoV-2 infections were found in the Southern region of NZ, supporting the elimination status of the country at the time this study was conducted. [**note: also staying with New Zealand, there is a serology study of the southern region of the country.**]
https://www.medrxiv.org/content/10.1101/2020.10.20.20215616v1

NEWLY REGISTERED CLINICAL TRIALS

- Done and dusted for this week!

CLINICAL TRIAL RESULTS

- Kidney manifestations are life-threatening conditions, such as end-stage renal disease (ESRD), especially when attributed to viral infections. The severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), is an emerging health problem worldwide, potentially affecting all organs, including the kidney. Most reports on kidney manifestations were conducted mostly on the adult and elderly population, and limited on children. Therefore, this study aims to analyse the correlation between kidney manifestations with the renal function of pediatric patients suffering from COVID-19. Methods. An observational analytic study was conducted in Hasan Sadikin General Hospital, Bandung, Indonesia, from March to August 2020. The demographic data, clinical signs, laboratory results, and notable kidney function were analysed, while the disease was classified as severe and nonsevere based on its clinical appearance. The Mann-Whitney test for nonparametric was used to analyze the collected data. Results. In this study, 16 COVID-19 children were selected as the research subjects, the median eGFR value in the severe group was lower (49.59 ml / minute / 1.73m2) compared to the nonsevere (113 ml / minute / 1.73m2), however, not statistically significant ($p = 0.521$). Significant high CRP and low thrombocyte levels were found in severe SARS-CoV-2 infection ($p<0.05$). Conclusion. A severe SARS-CoV-2 infection tends to affect the kidney, which is manifested as decreased glomerular filtration rate (GFR). [**note: here is the first paper from Indonesia that I've seen. Congrats to the researchers! This study looks at kidney manifestation of COVID-19 in children. It's a small set of patients but highlights something that needs to be looked out going forward.**]
https://www.medrxiv.org/content/10.1101/2020.10.20.20216440v1

DRUG DEVELOPMENT

- The COVID-19 pandemic caused by the emergent SARS-CoV-2 coronavirus threatens global public health and there is an urgent need to develop safe and effective vaccines. Here we report the generation and the preclinical evaluation of a novel replication-defective gorilla adenovirus-

vectored vaccine encoding the pre-fusion stabilized Spike (S) protein of SARS-CoV2. We show that our vaccine candidate, GRAd-COV2, is highly immunogenic both in mice and macaques, eliciting both functional antibodies which neutralize SARS-CoV-2 infection and block Spike protein binding to the ACE2 receptor, and a robust, Th1-dominated cellular response in the periphery and in the lung. We show here that the pre-fusion stabilized Spike antigen is superior to the wild type in inducing ACE2-interfering, SARS-CoV2 neutralizing antibodies. To face the unprecedented need for vaccine manufacturing at massive scale, different GRAd genome deletions were compared to select the vector backbone showing the highest productivity in stirred tank bioreactors. This preliminary dataset identified GRAd-COV2 as a potential COVID-19 vaccine candidate, supporting the translation of GRAd-COV2 vaccine in a currently ongoing Phase I clinical trial (NCT04528641). [**note: here is the preclinical data on a new gorilla adenovirus vaccine candidate (why can't they call it the King Kong vaccine?) from Italy. The full paper is interesting reading as they go into detail on isolation of the virus and how it was manipulated to make the vaccine strain.**]
https://www.biorxiv.org/content/10.1101/2020.10.22.349951v1

- Inhibitors of the protein-protein interaction (PPI) between the SARS-CoV-2 spike protein and ACE2, which acts as a ligand-receptor pair that initiates the viral attachment and cellular entry of this coronavirus causing the ongoing COVID-19 pandemic, are of considerable interest as potential antiviral agents. While blockade of such PPIs with small molecules is more challenging than with antibodies, small-molecule inhibitors (SMIs) might offer alternatives that are less strain- and mutation-sensitive, suitable for oral or inhaled administration, and more controllable / less immunogenic. Here, we report the identification of SMIs of this PPI by screening our compound-library that is focused on the chemical space of organic dyes. Among promising candidates identified, several dyes (Congo red, direct violet 1, Evans blue) and novel drug-like compounds (DRI-C23041, DRI-C91005) inhibited the interaction of hACE2 with the spike proteins of SARS-CoV-2 as well as SARS-CoV with low micromolar activity in our cell-free ELISA-type assays (IC50s of 0.2-3.0 µM); whereas, control compounds, such as sunset yellow FCF, chloroquine, and suramin, showed no activity. Protein thermal shift assays indicated that the SMIs identified here bind SARS-CoV-2-S and not ACE2. Selected promising compounds inhibited the entry of a SARS-CoV-2-S expressing pseudovirus into ACE2-expressing cells in concentration-dependent manner with low micromolar IC50s (6-30 µM). *This provides proof-of-principle evidence for the feasibility of small-molecule inhibition of PPIs critical for coronavirus attachment/entry and serves as a first guide in the search for SMI-based alternative antiviral therapies for the prevention and treatment of diseases caused by coronaviruses in general and COVID-19 in particular*. [**note: here are some *in vitro* inhibitors of the Spike-ACE2 interaction that blocks viral attachment and entry. The two experimental compounds have similar structures to the dyes mentioned.**]
https://www.biorxiv.org/content/10.1101/2020.10.22.351056v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- SARS-CoV-2 ORF3a is believed to form ion channels, which may be involved in the modulation of virus release, and has been implicated in various cellular processes like the up-regulation of fibrinogen expression in lung epithelial cells, downregulation of type 1 interferon receptor, caspase-dependent apoptosis, and increasing IFNAR1 ubiquitination. ORF3a assemblies as

homotetramers, which are stabilized by residue C133. A recent cryoEM structure of a homodimeric complex of ORF3a has been released. A lower-resolution cryoEM map of the tetramer suggests two dimers form it, arranged side by side. The dimer's cryoEM structure revealed that each protomer contains three transmembrane helices arranged in a clockwise configuration forming a six helices transmembrane domain. This domain's potential permeation pathway has six constrictions narrowing to about 0.1 nm in radius, suggesting the structure solved is in a closed or inactivated state. At the cytosol end, the permeation pathway encounters a large and polar cavity formed by multiple beta strands from both protomers, which opens to the cytosolic milieu. We modeled the tetramer following the arrangement suggested by the low-resolution tetramer cryoEM map. Molecular dynamics simulations of the tetramer embedded in a membrane and solvated with 0.5 M of KCl were performed. Our simulations show the cytosolic cavity is quickly populated by both K+ and Cl-, yet with different dynamics. K+ ions moved relatively free inside the cavity without forming proper coordination sites. In contrast, Cl- ions enter the cavity, and three of them can become stably coordinated near the intracellular entrance of the potential permeation pathway by an inter-subunit network of positively charged amino acids. Consequently, the central cavity's electrostatic potential changed from being entirely positive at the beginning of the simulation to more electronegative at the end. [**note: I don't know if I've seen a paper from Chile until today. This is an interesting look at the ORF3a protein structure and how chloride ions bind to it.**]
https://www.biorxiv.org/content/10.1101/2020.10.22.349522v1

- COVID-19 has had an unprecedented global impact in health and economy affecting millions of persons world-wide. To support and enable a collaborative response from the global research communities, we created a data collection for different public sources for anonymized patient clinical data, imaging datasets, molecular data as nucleotide and protein sequences for the SARS-CoV-2 virus, reports of count of cases and deaths per city/country, and other economic indicators in Databiology Lab (https://www.lab.databiology.net/) where researchers could access these data assets and use the hundreds of available open source bioinformatic applications to analyze them. These data assets are regularly updated and was used in a successful virtual 3-day hackathon organized by Databiology Ltd and Mindstream-AI where hundreds of attendees to work collaboratively to analyze these data collections. {**note: this is from a UK company and is large collection of public COVID-19 data. It may prove interesting to those who want to look further into SARS-CoV-2.**]
https://www.biorxiv.org/content/10.1101/2020.10.22.328864v1
- The interplay between the virus, infected cells and the immune ressponses to SARS-CoV-2 is still under debate. Extending the basic model of viral dynamics we propose here a formal approach to describe the neutralizing versus non-neutralizing scenarios and compare with the possible effects of antibody-dependent enhancement (ADE). The theoretical model is consistent with data available from the literature and conclusions show that, while both non-neutralizing scenarios and ADE give rise to similar final virus clearance, the non-neutralizing antibodies can induce permanent high levels of antibody production with documented unfavorable impact on the disease progression and outcome. We also discuss the implications on secondary infections. [**note: here is a theoretical model for adaptive humoral immunity; interesting reading.**]
https://www.medrxiv.org/content/10.1101/2020.10.21.20216713v1

DIAGNOSTIC DEVELOPMENT

- Nothing new.

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2020-10-24

Yesterday we had a clip from the Mozart Requiem where the mezzo soprano was Cecilia Bartoli. She has exquisite vocal control and trills like no other singer I've heard. Here is her interpretation of Handel's 'Ombra mai fu': https://www.youtube.com/watch?v=OdeOyrLHdSg From Mozart's 'Cosi fan Tutte' we have Fiordiligi's aria: https://www.youtube.com/watch?v=Wwpm5jegeYg and one of the songs that brought her early fame, Giordani's 'Caro mio ben', a song often assigned to beginning singers but difficult to pull off well: https://www.youtube.com/watch?v=-Hlk8EDA02M I have not heard this one done any better. Finally a clip from a documentary where she looks at the original score to Bellini's 'Norma' and sings the opening section of 'Casta Diva': https://www.youtube.com/watch?v=UCyes1CE2vU

The Washington Post explains what the mouthwash studies really mean. This seems prudent advice from one of the interviewees, "If it says rinse for 30 seconds and they're using it 10 times a day and they're using it for a minute at a time, there could be problems with their mucosa in their mouths and throats," Gansky said. "They could be creating a problem that we don't know about." The racial disparity in COVID-19 cases over time in Mississippi is interesting but also a cautionary tale. Mask wearing can save lives from a story that references the IHME model (see the Nature Medicine link). Both the J&J and AstraZeneca vaccine trials will resume as the clinical holds are lifted. The observed adverse events seem not to have been vaccine related. This is a bizarre and foolish decision by an Idaho county health board. It looks to me as the third wave of COVID-19 infections is hitting parts of the US hard. Tour companies are reinventing themselves. Let us hope your major appliances don't break down. I think this is a bit overblown as our over the oven microwave blew out back in early April and we were able to contact the appliance store and get a replacement delivered and installed within five days.

The New York Times also covers the increasing crush on hospital capacity. Here is the paper's take on the resumption of the two vaccine trials. I don't know what to make of this story about the closing of the National Vaccine Program Office means. It did not have primary responsibility for monitoring safety. This op-ed by the director of the Institute for Health Metrics and Evaluation is critical of the government's refusal to release important COVID-19 data. As one of my heroes, the late Senator Daniel Patrick Moynihan put it, 'there is too much secrecy in government!' This is a reminder to me to read his wonderful book "Secrecy"; things like this never end well.

Nature Medicine has the latest forecast for COVID-19 in the US by the IHME. Here is an interesting article on making antibodies for COVID-19 treatment cheaper.

Science has a very good article on the engines of SARS-CoV-2 spread. This is well written and easy to understand. Here is an overview on the susceptibility to severe COVID-19. These two Harvard epidemiologists will help you understand COVID-19 vaccine efficacy. Speaking of vaccines (and who isn't these days), here is a structural analysis of the Spike protein that is in the Novavax experimental COVID-19 that has moved into Phase 2/3 trials. There are two papers showing that Neuropilin-1 facilitates SARS-CoV-2 entry and infectivity HERE and HERE.

STAT have an article discussing whether FDA is getting 'cold feet' over the EUA for COVID-19 vaccines. Here is their take on the lifting of the clinical holds on the J&J and AstraZeneca experimental vaccines.

The Lancet have a research article on the Dutch experience with ventilation management for hospitalized COVID-19 patients. *Predictors of 28-day mortality were gender, age, tidal volume, respiratory system compliance, arterial pH, and heart rate on the first day of invasive ventilation*. Here is an opinion piece on deciphering early clinical trials with a focus on dexamethasone and remdesivir. *"…although large randomised controlled trials allow for rapid and statistically powerful results, their preprint releases should be interpreted with caution, and smaller, more granular trials with more thorough data collection and more nuanced outcomes should not be abandoned nor prematurely terminated. Searches for magic bullets should continue; we lack drugs specifically designed to target SARS-CoV-2. Combination therapies with antiviral and anti-inflammatory agents will bring new challenges. The results of these searches will thus require careful, committed scrutiny, and our patients deserve sober analyses*."

Wow! For a Saturday there is a lot to read and digest!!!

MODELING

- We study transmission of COVID-19 using five well-documented case studies : a Washington state church choir, a Korean call center, a Korean exercise class, and two different Chinese bus trips. In all cases the likely index patients were pre-symptomatic or mildly symptomatic, which is when infective patients are most likely to interact with large groups of people. An estimate of N 0 , the characteristic number of COVID-19 virions needed to induce infection in each case, is found using a simple physical model of airborne transmission. We find that the N 0 values are similar for five COVID-19 superspreading cases (~300-2,000 viral copies) and of the same order as influenza A. Consistent with the recent results of Goyal et al , *these results suggest that viral loads relevant to infection from presymptomatic or mildly symptomatic individuals may fall into a narrow range, and that exceptionally high viral loads are not required to induce a superspreading event [1,2] . Rather, t he accumulation of infective aerosols exhaled by a typical pre-symptomatic or mildly symptomatic patient in a confined, crowded space (amplified by poor ventilation, particularly activity like exercise or singing, or lack of masks) for exposure times as short as one hour are sufficient. We calculate that talking and breathing release ~460 N 0 and ~10 N 0 (quanta)/hour, respectively, providing a basis to estimate the risks of everyday activities*. Finally, we provide a calculation which motivates the observation that fomites appear to account for a smallpercentage of total COVID-19 infection events. [**note: Here is a model for superspreading events without superspreaders based on information from real events.**] https://www.medrxiv.org/content/10.1101/2020.10.21.20216895v1
- There is considerable debate about the rate of antibody waning after SARS-CoV-2 infection, raising questions around long-term immunity following both natural infection and vaccination. We undertook prospective serosurveillance in a large cohort of healthy adults from the start of the epidemic in England. Methods The serosurveillance cohort included office and laboratory-based staff and healthcare workers in 4 sites in England, who were tested monthly for SARS-CoV-2 spike protein and nucleoprotein IgG between 23rd March and 20th August 2020.

Antibody levels from 21 days after a positive test were modelled using mixed effects regression models. Findings In total, 2247 individuals were recruited and 2014 (90%) had 3-5 monthly antibody tests. Overall, 272 (12.1%) of individuals had at least one positive/equivocal spike protein IgG result, with the highest proportion in a hospital site (22%), 14% in London and 2.1% in a rural area. Results were similar for nucleoprotein IgG. Following a positive result, 39/587 (6.6%) tested negative for nucleoprotein IgG and 52/515 (10.1%) for spike protein IgG. Nucleoprotein IgG declined by 6.4% per week (95% CI, 5.5-7.4%; half-life, 75 [95% CI, 66-89] days) and spike protein IgG by 5.8% (95% CI, 5.1-6.6%; half-life, 83 [95% CI, 73-96] days). Conclusions *Over the study period SARS-CoV-2 seropositivity was 8-10% overall and up to 21% in clinical healthcare workers. In seropositive individuals, nucleoprotein and spike protein IgG antibodies declined with time after infection and 50% are predicted to fall below the positive test threshold after 6 months*. [**note: here is a serology surveillance study of UK public health workers. A time dependent decline in antibodies was seen.**]
https://www.medrxiv.org/content/10.1101/2020.10.21.20216689v1

- Population-wide facial masking decreases COVID-19 transmission but may also decrease the severity of disease by reducing the viral inoculum to which the wearer is exposed. The mortality of COVID-19 infection decreased in the U.S. in the second wave over the summer of 2020 compared to the first, but reasons for declining severity of disease have not been fully elucidated. Objective: To determine if facial mask mandates instituted in U.S. counties over the spring and summer of 2020 were associated with declining severity of infection as measured by the number of hospitalizations for COVID-19. Design: Data on hospitalizations due to COVID-19; testing access determined by number of tests performed per day per 100,000 people; new cases per day normalized by population; measures of population mobility to control for other non-pharmaceutical interventions such as lockdowns, social distancing, and business closures; age categories in each census tract; and dates of masking mandates in U.S. counties were all obtained from open-sourced epidemiologic datasets. We used a staggered difference-in-difference study design to assess the impact of the introduction of mask mandates (defined as the treatment) on the proportion of hospitalizations due to COVID-19 per week from March 10-September 16, 2020. Setting: U.S. counties with available full datasets on relevant COVID-19 metrics Exposure: Mask mandates Main outcome: Proportion of hospitalizations due to COVID-19 Results: Using data from 1083 counties (34% of U.S. counties, 82% of U.S. population) from 49 states, we found a statistically significant drop in hospitalization rates due to COVID-19 up to 12 weeks following county mask mandates of 7.13 (95% CI: -4.19, -10.1) percentage points, after controlling for age categories by county, testing access, numbers of cases, and population mobility. Conclusion and Relevance: *Facial masking may decrease COVID-19 severity by decreasing the viral inoculum to which individuals are exposed. Mask mandates across 1083 counties in the U.S. in 49 states decreased hospitalization rates from COVID-19 even when controlling for other factors that could impact disease severity, including age, testing access, number of cases, and mobility (as a proxy for other non-Pharmaceutical interventions such as sheltering-in-place). This study adds to the growing evidence for the impact of masking on disease severity and on the utility of population-wide facial masking for COVID-19 pandemic control*. [**note: more on how masks help out in the fight against COVID-19. Is it too little to ask of people just to MASK UP?**]
https://www.medrxiv.org/content/10.1101/2020.10.21.20208728v1

- Testing strategies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in school settings are needed to assess the efficacy of infection mitigation strategies and inform school reopening policies. We hypothesized that supervised serial self-collected non-nasopharyngeal testing in summer camp settings would be acceptable and feasible. Methods: We performed a cohort study at two urban day camps for kindergarten-8th graders in June and July 2020. Eligible participants were campers, up to two adult household contacts, and camp staff. We assessed participation rates for providing, at two time points, supervised, self-collected anterior nares samples for reverse transcription polymerase chain reaction (RT-PCR) and saliva samples for antibody testing. We qualitatively assessed testing feasibility and adherence to stated camp infection mitigation strategies. Results: 76% (186/246) of eligible participants consented. The cohort completing both rounds of testing (n=163) comprised 67 campers, 76 household contacts, and 20 staff. *Among those present, 100% of campers and staff completed test collection at both time points. Testing was feasible to implement, including staff participation supervising camper test collection. No virus was detected by RT-PCR; seven participants had antibodies. Observed adherence to stated camp mitigation policies for masking, physical distancing, and stable cohorting was generally high. Conclusions: Supervised, self-collected serial anterior nasal and saliva-based SARS-CoV-2 testing was acceptable, with successful repeated participation by children ages 5-14. This strategy for testing and the observed infection mitigation practices comprise potential core components for safe school reopening*. [**note: here is a testing strategy that was used over the summer at two urban day camps that might translate more broadly to use in schools.**]
  https://www.medrxiv.org/content/10.1101/2020.10.21.20214338v1

NEWLY REGISTERED CLINICAL TRIALS

- Already done this week!

CLINICAL TRIAL RESULTS

- To describe the spectrum of neurological and psychiatric complications in patients with Covid-19 seen in a multidisciplinary center over six months. Methods: We conducted a retrospective, observational study on all patients showing neurological or psychiatric symptoms in the context of Covid-19 seen in the Department of Neurology and Psychiatry of the APHP-Sorbonne University. We collected demographic data, medical and treatment history, comorbidities, symptoms, date of onset, and severity of Covid-19 infection, neurological and psychiatric symptoms, neurological and psychiatric examination data and, when available, results from cerebrospinal fluid (CSF) analysis, brain magnetic resonance (MRI) imaging, 18-fluorodesoxyglucose-position emission computed tomography (FDG-PET/CT)), electroencephalography (EEG) and electroneuromyography (ENMG). Results: 245 patients were included in the analysis. One-hundred fourteen patients (47%) were admitted to the intensive care unit (ICU) and 10 (4%) died. *The most frequently reported neuropsychiatric symptoms were motor deficit (41%), cognitive disturbance (35%), impaired consciousness (26%), psychiatric disturbance (24%), headache (20%) and behavioral disturbance (18%). The most frequent syndromes diagnosed were encephalopathy (43%), critical illness polyneuropathy and myopathy (26%), isolated psychiatric disturbance (18%), and cerebrovascular disorders (16%). No patients showed evidence of SARS-CoV-2 in their CSF. Encephalopathy was associated with greater age*

and higher risk of death. Critical illness neuromyopathy was associated with an extended stay in the ICU. Conclusions: The majority of the neuropsychiatric complications recorded could be imputed to critical illness, intensive care and systemic inflammation, which contrasts with the paucity of more direct SARS-CoV-2-related complications or post-infection disorders. [**note: here is a description of neuropsychiatric complications in COVID-19 patients from one hospital system in France.**] https://www.medrxiv.org/content/10.1101/2020.10.21.20216747v1

- The antiparasitic drug nitazoxanide is widely available and exerts broad-spectrum antiviral activity in vitro. However, there is no evidence of its impact on SARS-CoV-2 infection. In a multicenter, randomized, double-blind, placebo-controlled trial, adult patients who presented up to 3 days after onset of Covid-19 symptoms (dry cough, fever, and/or fatigue) were enrolled. After confirmation of SARS-CoV2 infection by RT-PCR on nasopharyngeal swab, patients were randomized 1:1 to receive either nitazoxanide (500 mg) or placebo, TID, for 5 days. The primary outcome was complete resolution of symptoms. Secondary outcomes were viral load, general laboratory tests, serum biomarkers of inflammation, and hospitalization rate. Adverse events were also assessed. From June 8 to August 20, 2020, 1,575 patients were screened. Of these, 392 (198 placebo, 194 nitazoxanide) were analyzed. Median time from symptom onset to first dose of study drug was 5 (4-5) days. *At the 5-day study visit, symptom resolution did not differ between the nitazoxanide and placebo arms. However, at the 1-week follow-up, 78% in the nitazoxanide arm and 57% in the placebo arm reported complete resolution of symptoms (p=0.048). Swabs collected were negative for SARS-CoV-2 in 29.9% of patients in the nitazoxanide arm versus 18.2% in the placebo arm (p=0.009). Viral load was also reduced after nitazoxanide compared to placebo (p=0.006). No serious adverse events were observed. In patients with mild Covid-19, symptom resolution did not differ between the nitazoxanide and placebo groups after 5 days of therapy*. However, early nitazoxanide therapy was safe and reduced viral load significantly. [**note: this is the first result I've seen on nitazoxanide and it may have a modest treatment effect on reducing viral load. Study is from Brazil.**] https://www.medrxiv.org/content/10.1101/2020.10.21.20217208v1
- Coronavirus disease 2019 (Covid-19) pneumonia is often associated with hyperinflammation. Safety and efficacy of the anti-interleukin-6 receptor antibody tocilizumab was evaluated in patients hospitalized with Covid-19 pneumonia. Methods: Nonventilated patients hospitalized with Covid-19 pneumonia were randomized (2:1) to tocilizumab (8 mg/kg intravenous) or placebo plus standard care. Sites enrolling high-risk and minority populations were emphasized. The primary endpoint was cumulative proportion of patients requiring mechanical ventilation or who had died by Day 28. Results: Of 389 randomized patients, 249 patients received tocilizumab and 128 received placebo in the modified intent-to-treat population (Hispanic/Latino, 56.0%; Black/African American, 14.9%; American Indian/Alaska Native, 12.7%; White, 12.7%; other/unknown, 3.7%). The cumulative proportion (95% confidence interval [CI]) of patients requiring mechanical ventilation or who had died by Day 28 was 12.0% (8.52% to 16.86%) and 19.3 % (13.34% to 27.36%) for the tocilizumab and placebo arms, respectively (log-rank P=0.0360; hazard ratio, 0.56 [95% CI, 0.33 to 0.97]). Median time to clinical failure up to Day 28 favored tocilizumab over placebo (hazard ratio 0.55 [95% CI, 0.33 to 0.93]). All-cause mortality by Day 28 was 10.4% with tocilizumab and 8.6% with placebo (weighted difference, 2.0% [95% CI, -5.2% to 7.8%). In the safety population, serious adverse events occurred in 15.2% of tocilizumab patients (38/250 patients) and 19.7% of placebo patients (25/127). Conclusions: *This*

trial demonstrated the efficacy and safety of tocilizumab over placebo in reducing the likelihood of progression to requiring mechanical ventilation or death in nonventilated patients hospitalized with Covid-19 pneumonia. [**note: this is a Genentech funded study of tocilizumab and it appears that there is a treatment effect in nonventilated COVID-19 patients with pneumonia.]** https://www.medrxiv.org/content/10.1101/2020.10.21.20210203v1

- Coronavirus disease 19 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Understanding the clinical correlations of antibodies produced by infected individuals will be critical for incorporating antibody results into clinical management. This study was an observational cohort study to evaluate antibody responses in individuals with PCR-confirmed COVID-19, including 48 hospitalized patients diagnosed with COVID-19 by real-time polymerase chain reaction (RT-PCR) at a large tertiary care medical center. Serum samples were obtained from patients at various time points during the disease course and tested for IgM and IgG antibodies against SARS-CoV-2. Medical records were reviewed, and antibody levels were compared with clinical and laboratory findings. Patients did not have high levels of antibodies within one week of symptoms, but most had detectable IgM and IgG antibodies between 8 and 29 days after onset of symptoms. Some individuals did not develop measurable levels of IgM or IgG antibodies. IgM antibodies were associated with elevated ALT, but there were no other significant associations. We did not observe significant associations of SARS-CoV-2 antibodies with clinical outcomes, including intubation and death. SARS-CoV-2 IgM and IgG antibodies were unlikely to be detected in the first week of infection or in severely immunocompromised individuals. *Although we did not observe associations with clinical outcomes, IgM antibodies were associated with higher ALT levels. Antibody production reflects the virus-specific immune response, which is important for immunity but also drives pathology, and antibody levels may be important for guiding treatment of individuals with COVID-19*. [**note: here is more on the clinical correlation antibody response in COVID-19 patients. It is still weird that they as others are seeing some patients with little antibody response.**] https://www.medrxiv.org/content/10.1101/2020.10.22.20213207v1
- Severe SARS-CoV-2 infection is linked to the presence of autoantibodies against multiple targets, including phospholipids and type-I interferons. *We recently identified activation of an autoimmune-prone B cell response pathway as correlate of severe COVID-19, raising the possibility of de novo autoreactive antibody production during the antiviral response. Here, we identify autoreactive antibodies as a common feature of severe COVID-19, identifying biomarkers of tolerance breaks that may indicate aggressive immunomodulation*. [**note: more on how the immune system goes out of whack. These Emory researchers find evidence for autoreactive antibodies.**] https://www.medrxiv.org/content/10.1101/2020.10.21.20216192v1

DRUG DEVELOPMENT

- The energetics of the folding of a single-stranded nucleic acid into a stem-loop structure depend on both the composition and order of its bases. Composition tends to reflect genome-wide evolutionary pressures. Order better reflects local pressures. *Base order is likely to be conserved when encoding a function critical for survival. The base order-dependent component of the folding energy has shown that a highly conserved region in HIV-1 genomes associates with an RNA structure. This corresponds to a packaging signal that is specifically recognized by the nucleocapsid domain of the Gag polyprotein. Long viewed as a potential HIV-1 "Achilles heel,"*

the signal can be targeted by a recently described antiviral compound (NSC 260594) or by synthetic oligonucleotides. Thus, a conserved base-order-rich region of HIV-1 may facilitate therapeutic attack. Although SARS-CoV-2 differs in many respects from HIV-1, the same technology displays regions with a high base order-dependent folding energy component, which are also highly conserved. This indicates structural invariance (SI) sustained by natural selection. While the regions are often also protein-encoding (e.g. NSP3, ORF3a), we suggest that their nucleic acid level functions, such as the ribosomal frameshifting element (FSE) that facilitates differential expression of 1a and 1ab polyproteins, can be considered potential "Achilles heels" for SARS-CoV-2 that should be susceptible to therapies like those envisaged for AIDS. The region of the FSE scored well, but higher SI scores were obtained in other regions, including those encoding NSP13 and the nucleocapsid (N) protein. [**note: these two researchers believe they may have identified a potential Achilles heel of SARS-CoV-2. It is based some earlier research on HIV.**] https://www.biorxiv.org/content/10.1101/2020.10.22.343673v1

- The search for vaccines that protect from severe morbidity and mortality as a result of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19) is a race against the clock and the virus. Several vaccine candidates are currently being tested in the clinic. Inactivated virus and recombinant protein vaccines can be safe options but may require adjuvants to induce robust immune responses efficiently. In this work we describe the use of a novel amphiphilic imidazoquinoline (IMDQ-PEG-CHOL) TLR7/8 adjuvant, consisting of an imidazoquinoline conjugated to the chain end of a cholesterol-poly(ethylene glycol) macromolecular amphiphile). This amphiphile is water soluble and exhibits massive translocation to lymph nodes upon local administration, likely through binding to albumin. IMDQ-PEG-CHOL is used to induce a protective immune response against SARS-CoV-2 after single vaccination with trimeric recombinant SARS-CoV-2 spike protein in the BALB/c mouse model. Inclusion of amphiphilic IMDQ-PEG-CHOL in the SARS-CoV-2 spike vaccine formulation resulted in enhanced immune cell recruitment and activation in the draining lymph node. IMDQ-PEG-CHOL has a better safety profile compared to native soluble IMDQ as the former induces a more localized immune response upon local injection, preventing systemic inflammation. Moreover, IMDQ-PEG-CHOL adjuvanted vaccine induced enhanced ELISA and in vitro microneutralization titers, and a more balanced IgG2a/IgG1 response. To correlate vaccine responses with control of virus replication in vivo, vaccinated mice were challenged with SARS-CoV-2 virus after being sensitized by intranasal adenovirus-mediated expression of the human angiotensin converting enzyme 2 (ACE2) gene. *Animals vaccinated with trimeric recombinant spike protein vaccine without adjuvant had lung virus titers comparable to non-vaccinated control mice, whereas animals vaccinated with IMDQ-PEG-CHOL-adjuvanted vaccine controlled viral replication and infectious viruses could not be recovered from their lungs at day 4 post infection. In order to test whether IMDQ-PEG-CHOL could also be used to adjuvant vaccines currently licensed for use in humans, proof of concept was also provided by using the same IMDQ-PEG-CHOL to adjuvant human quadrivalent inactivated influenza virus split vaccine, which resulted in enhanced hemagglutination inhibition titers and a more balanced IgG2a/IgG1 antibody response. Enhanced influenza vaccine responses correlated with better virus control when mice were given a lethal influenza virus challenge. Our results underscore the potential use of IMDQ-PEG-CHOL as an adjuvant to achieve protection after single immunization with recombinant protein and inactivated virus vaccines against respiratory viruses, such as SARS-*

CoV-2 and influenza viruses. {**note: the Mt. Sinai folks have been very busy! Here is a novel adjuvant that may be useful in vaccine preparations.**
https://www.biorxiv.org/content/10.1101/2020.10.23.344085v1

- The devastating SARS-CoV-2 pandemic demands rapid vaccine development and large scale production to meet worldwide needs. mRNA vaccines have emerged as one of the most promising technologies to address this unprecedented challenge. Here, we show preclinical data for our clinical candidate CVnCoV, a lipid nanoparticle (LNP) encapsulated non-modified mRNA vaccine that encodes the full length, pre-fusion stabilised SARS-CoV-2 Spike (S) protein. S translated from CVnCoV is cleaved, post-translationally modified, and presented on the cell surface, highlighting the ability of mRNA vaccines to mimic antigen presentation during viral infection. Immunisation with CVnCoV induced strong humoral responses with high titres of virus neutralizing antibodies in mice and hamsters and robust CD4+ and CD8+ T cell responses in mice. Most importantly, vaccination with CVnCoV fully protected hamster lungs from challenge with wild type SARS-CoV-2. To gain insights in the risk of vaccine-enhanced disease, hamsters vaccinated with a suboptimal dose of CVnCoV leading to breakthrough viral replication were analysed for signs of vaccine-enhanced disease. No evidence of increased viral replication or exacerbated inflammation and damage to viral target organs was detectable, giving strong evidence for a favourable safety profile of CVnCoV. Overall, data presented here provide evidence that CVnCoV represents a potent and safe vaccine candidate against SARS-CoV-2. [**note: here is animal data on the CureVac mRNA vaccine. This one is also in human clinical trials.**] https://www.biorxiv.org/content/10.1101/2020.10.23.351775v1
- The novel SARS-CoV-2 virus emerged in December 2019 and has few effective treatments. We applied a computational drug repositioning pipeline to SARS-CoV-2 differential gene expression signatures derived from publicly available data. We utilized three independent published studies to acquire or generate lists of differentially expressed genes between control and SARS-CoV-2-infected samples. Using a rank-based pattern matching strategy based on the Kolmogorov-Smirnov Statistic, the signatures were queried against drug profiles from Connectivity Map (CMap). We validated sixteen of our top predicted hits in live SARS-CoV-2 antiviral assays in either Calu-3 or 293T-ACE2 cells. Validation experiments in human cell lines showed that 11 of the 16 compounds tested to date (including clofazimine, haloperidol and others) had measurable antiviral activity against SARS-CoV-2. These initial results are encouraging as we continue to work towards a further analysis of these predicted drugs as potential therapeutics for the treatment of COVID-19. [**note: this is a joint effort from UCSF and Mt Sinai groups who have published previous drug discovery papers. You will need to download the paper to see the entire list of drugs they identify though I will single out two interesting ones: fluticasone and lansoprazole. I am running a small clinical trial of '1' with Flonase right now!!!!**]
https://www.biorxiv.org/content/10.1101/2020.10.23.352666v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- SARS-CoV-2 nucleocapsid (N) protein is highly expressed upon infection and is essential for viral replication, making it a promising target for both antiviral drug and vaccine development. Here, starting from a functional proteomics workflow, we initially catalogued the protein-protein interactions of 21 SARS-CoV-2 proteins in HEK293 cells, finding that the stress granule resident proteins G3BP1 and G3BP2 co-purify with N with high specificity. We demonstrate that N

protein expression of in human cells sequesters G3BP1 and G3BP2 through its physical interaction with these proteins, attenuating stress granule (SG) formation. The ectopic expression of G3BP1 in N-expressing cells was sufficient to reverse this phenotype. Since N is an RNA-binding protein, we performed iCLIP- sequencing experiments in cells, with or without exposure to oxidative stress, to identify the host RNAs targeted by N. *Our results indicate that SARS-CoV-2 N protein binds directly to thousands of host mRNAs under both conditions. Like the G3BPs stress granule proteins, N was found to predominantly bind its target mRNAs in their 3UTRs. RNA sequencing experiments indicated that expression of N results in wide-spread gene expression changes in both unstressed and oxidatively stressed cells. We suggest that N regulates host gene expression by both attenuating stress granules and binding directly to target mRNAs*. [**note: here is more on the Nucleocapsid protein. I still wonder if not putting the N protein into some of the vaccine vectors is a mistake.**]
https://www.biorxiv.org/content/10.1101/2020.10.23.342113v1

- he SARS-CoV-2 spike (S) glycoprotein trimer mediates virus entry into host cells and cytopathic effects. We studied the contribution of several S glycoprotein features to these functions, focusing on those that differ among related coronaviruses. Acquisition of the furin cleavage site by the SARS-CoV-2 S glycoprotein decreased virus stability and infectivity, but greatly enhanced the ability to form lethal syncytia. Notably, the D614G change found in globally predominant SARS-CoV-2 strains restored infectivity, modestly enhanced responsiveness to the ACE2 receptor and susceptibility to neutralizing sera, and tightened association of the S1 subunit with the trimer. Apparently, two unique features of the SARS-CoV-2 S glycoprotein, the furin cleavage site and D614G, have evolved to balance virus infectivity, stability, cytopathicity and antibody vulnerability. Although the endodomain (cytoplasmic tail) of the S2 subunit was not absolutely required for virus entry or syncytium formation, alteration of palmitoylated cysteine residues in the cytoplasmic tail decreased the efficiency of these processes. *As proteolytic cleavage contributes to the activation of the SARS-CoV-2 S glycoprotein, we evaluated the ability of protease inhibitors to suppress S glycoprotein function. Matrix metalloprotease inhibitors suppressed S-mediated cell-cell fusion, but not virus entry. Synergy between inhibitors of matrix metalloproteases and TMPRSS2 suggest that both proteases can activate the S glycoprotein during the process of syncytium formation. These results provide insights into SARS-CoV-2 S glycoprotein-host cell interactions that likely contribute to the transmission and pathogenicity of this pandemic agent*. [**note: here is more on the Spike protein and how the main functions are impacted by the D614G mutation.**]
https://www.biorxiv.org/content/10.1101/2020.10.22.351569v1
- Angiotensin-converting enzyme 2 (ACE2) has been suggested as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry to cause coronavirus disease 2019 (COVID-19). However, no ACE2 inhibitors have shown definite beneficiaries for COVID-19 patients, applying the presence of another receptor for SARS-CoV-2 entry. *Here we show that ACE2 knockout dose not completely block virus entry, while TfR directly interacts with virus Spike protein to mediate virus entry and SARS-CoV-2 can infect mice with over-expressed humanized transferrin receptor (TfR) and without humanized ACE2. TfR-virus co-localization is found both on the membranes and in the cytoplasma, suggesting SARS-CoV-2 transporting by TfR, the iron-transporting receptor shuttling between cell membranes and cytoplasma.* Interfering TfR-Spike interaction blocks virus entry to exert significant anti-viral effects. Anti-TfR antibody (EC50 16.6

nM) shows promising anti-viral effects in mouse model. Collectively, this report indicates that TfR is another receptor for SARS-CoV-2 entry and a promising anti-COVID-19 target. [**note: these Chinese scientists suggest there may be a second receptor for SARS-CoV-2 cell entry. This may not be good news.**] https://www.biorxiv.org/content/10.1101/2020.10.23.350348v1

DIAGNOSTIC DEVELOPMENT

- SARS-CoV-2 diagnostics that report viral RNA concentrations can be used to determine a patient's stage of infection, but this potential has not yet been realized due to a lack of prospective longitudinal data to calibrate such inferences. Here, we report the viral RNA trajectories for 68 individuals using quantitative PCR testing. On average, symptomatic and asymptomatic individuals reached similar peak viral RNA concentrations (22.2 Ct, 95% credible interval [19.1, 25.1] vs. 22.4 Ct [20.2, 24.5]) within similar amounts of time (2.9 days [0.7, 4.7] vs. 3.0 days [1.3, 4.3]), but acute shedding lasted longer for symptomatic individuals (10.5 days [6.5, 14.0] vs. 6.7 days [3.2, 9.2]). A second test within 2 days after an initial positive PCR result reliably indicated whether viral RNA concentration was increasing, decreasing, or in a low-level persistent phase. *Quantitative viral RNA assessment, informed by viral trajectory, can improve algorithms for clinical and public health management*. [**note: here is study of viral dynamics of SARS-CoV-2 infection ascertained by repeat PCR testing.**] https://www.medrxiv.org/content/10.1101/2020.10.21.20217042v1

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2020-10-25

My favorite of the three Mozart/da Ponte operas is not what you might think. Don Giovanni is a little too jaded for me and Marriage of Figaro is too flippant. I prefer Cosi fan tutte because of its ambiguity. I give full credit to the Pittsburgh Opera for staging a pandemic version of the opera. Yes, it is heavily cut but that is OK when you can see live performances happening. Enjoy this one!!! https://www.youtube.com/watch?v=wwbL5objneE

The New York Times has a story about why school children may not be spreading SARS-CoV-2. I am not convinced. The CDC has tips on how to vote safely if you are doing this in person. Dr. Fauci suggests a national mask mandate might be in order. Gyms have reopened in NY City but membership is down. Cases of COVID-19 continue to rise in many areas.

The Washington Post asks why we don't have any home COVID-19 test kits? I wonder the same thing. Belgium is short of teachers, police and healthcare workers because of COVID-19. Here is another voice from the pandemic, a Minneapolis woman who founded a food kitchen and charity organization. Here is advice for those having 'long-haul' COVID-19 from three people who have had similar symptoms from other infections. There seems to be some controversy about the recent study on airline safety regarding SARS-CoV-2 transmission.

Because Sunday is usually a slow day for new papers, I will be posting new clinical trials instead of Wednesday.

MODELING

- Objectives: The objectives of this study were to identify demographic, work-related and other predictors for clinically significant psychological distress, including PTSD, depression, and/or anxiety during the COVID-19 pandemic in UK frontline health and social care workers (HSCWs), and to compare rates of PTSD, depression and anxiety across different groups of HCSWs. Design: An online survey was conducted in the weeks following the initial peak in cases (27 May to 23 July 2020). Setting: The participants worked in a variety of healthcare roles UK hospitals, nursing or care homes and community settings. Participants: A convenience sample (n=1194) of frontline UK health and social care workers completed the survey (including allied healthcare professionals, carers, clinical support staff, nurses and midwives, and other health and social care roles). Main outcome measures: PTSD was assessed using the PTSD subscale of the International Trauma Questionnaire (ITQ); Depression assessed using the Patient Health Questionnaire-9 (PHQ-9); Anxiety was assessed using the Generalized Anxiety Disorder Scale (GAD-7). Results: Logistic regression analyses examined predictors for depression, anxiety and PTSD separately, and also investigated the predictors of meeting the criteria for at least one of the three conditions. Over 57% of respondents met the threshold for clinically significant PTSD, anxiety or depression, and symptom levels were reasonably high and comparable across occupational groups. Participants who were more concerned about infecting others, who felt they could not talk with their managers, who reported feeling stigmatised due to their role and who had not had reliable access to personal protective equipment (PPE) were more likely to meet criteria for a clinically significant mental disorder. Being redeployed during the pandemic, and having had COVID were associated with a higher likelihood of meeting criteria for PTSD. Higher household income was associated with reduced odds for a mental disorder. Conclusions: This study identifies predictors of clinically significant distress during COVID-19 and highlights the need for reliable access to PPE. Further research should investigate mental disorders in under-represented HSCW groups and examine barriers to communication between managers and staff. Identifying risk factors for PTSD, depression and anxiety among HSCWs, and providing treatment for those who need it, is critical given that subsequent waves of COVID-19 and other healthcare crises are inevitable. [**note: here is a study on PTSD, depression, and anxiety in UK frontline healthcare workers.]**
  https://www.medrxiv.org/content/10.1101/2020.10.21.20216804v1
- A mathematical model of COVID-19 is presented where the decision to increase or decrease social distancing is modelled dynamically as a function of the measured active and total cases as well as the perceived cost of isolating. Along with the cost of isolation, we define a healthcare cost and a total cost. We explore these costs by adjusting parameters that could change with policy decisions. We observe that minimum costs are not always associated with increased spending and increased vigilance which is due to the desire for people to not distance and the fatigue they experience when they do. *We demonstrate that an increased in the number of lock-downs, each of shorter duration can lead to minimal costs. Our results are compared to case data in Ontario, Canada from March to August 2020 and details of extracting the results to other regions is presented*. [**note: this is from Toronto and models the cost and social dynamics linked to social distancing.**]
  https://www.medrxiv.org/content/10.1101/2020.10.21.20217158v1

NEWLY REGISTERED CLINICAL TRIALS

- The objectives of the trial are to evaluate the efficacy and safety of trimodulin as add-on therapy to standard of care (SoC) compared to placebo treatment in adult hospitalized subjects with severe COVID-19. [**note: this is from Spain and the company is Biotest. This is an antibody preparation.**] NCT04576728
- The proposed trial will obtain preliminary data on the feasibility of studying RTB101 as compared to placebo for COVID-19 post-exposure prophylaxis in adults age ≥ 65 years to inform the design of a subsequent pivotal trial. [**note: this is from Restorbio and I don't know much about the compound other than what is HERE and that this was licensed from Novartis. Maybe there was a reason Novartis did not follow up on this.**] NCT04584710
- Randomized, double-blind prospective trial to test the efficacy and acceptability of therapeutic, antiseptic mouth rinses to inactivate severe acute respiratory syndrome coronavirus (SARS-CoV-2) in saliva of COVID-19 positive patients aged 18-65 years old. All mouthrinses are commercially available and will be used according to on-label instructions. Patients will be randomized to a mouthrinse and will be asked to give a saliva sample immediately before and after a one minute mouthwash. Saliva samples will be collected from patients at 15 minute intervals thereafter up to an hour (15, 30, 45 and 60 minutes). The samples will be stored and used for real-time reverse transcription polymerase chain reaction (RT-PCR) detection of viral SARS-CoV-2 RNA and viral infectivity assays. Patients will also complete a short-survey on the taste and experience of using the mouthwash. This study involves 480 subject participants and one, 75-90 minute visit. [**note: here is a Univ of North Carolina trial for all you mouthwash fans!!! Five commercial preparations will be tested.]** NCT04584684
- ADM03820 is indicated for the treatment and prevention of SARS-CoV-2 (COVID-19) in adults. The primary purpose of this study is to assess the safety of ADM03820 in healthy male and female subjects compared to placebo. [**note: this is another monoclonal antibody cocktail from Ology Bioservices.**] NCT04592549
- The purpose of this study is to test the safety and tolerability of HFB30132A when it is given by intravenously to healthy participants. Blood tests will be done to check how much HFB30132A is in the bloodstream and how long the body takes to eliminate it. Participation may include up to ten visits to the study center. [**note: this study is from HiFiBIO Therapeutics and the drug appears to be a cloned neutralizing antibody.]** NCT04590430

CLINICAL TRIAL RESULTS

- Abstract: Introduction: Coronavirus disease-19 (COVID-19) has caused a marked increase in all-cause deaths in the United States, mostly among adults aged 65 and older. Because younger adults have far lower infection fatality rates, less attention has been focused on the mortality burden of COVID-19 in this demographic. Methods: We performed an observational cohort study using public data from the National Center for Health Statistics at the United States Centers for Disease Control and Prevention, and CDC Wonder. We analyzed all-cause mortality among adults ages 25-44 during the COVID-19 pandemic in the United States. Further, we compared COVID-19-related deaths in this age group during the pandemic period to all drug overdose deaths and opioid-specific overdose deaths in each of the ten Health and Human Services (HHS) regions during the corresponding period of 2018, the most recent year for which data are available. Results: *As of September 6, 2020, 74,027 all-cause deaths occurred among persons ages 25-44 years during the period from March 1st to July 31st, 2020, 14,155 more than*

during the same period of 2019, a 23% relative increase (incident rate ratio 1.23; 95% CI 1.21-1.24), with a peak of 30% occurring in May (IRR 1.30; 95% CI 1.27-1.33). In HHS Region 2 (New York, New Jersey), HHS Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, Texas), and HHS Region 9 (Arizona, California, Hawaii, Nevada), COVID-19 deaths exceeded 2018 unintentional opioid overdose deaths during at least one month. Combined, 2,450 COVID-19 deaths were recorded in these three regions during the pandemic period, compared to 2,445 opioid deaths during the same period of 2018. Meaning: We find that COVID-19 has likely become the leading cause of death (surpassing unintentional overdoses) among young adults aged 25-44 in some areas of the United States during substantial COVID-19 outbreaks. [**note: this is a study of COVID-19 related mortality in the 25-44 age cohort. Sobering statistics indeed.**] https://www.medrxiv.org/content/10.1101/2020.10.21.20217174v1

DRUG DEVELOPMENT

- High ivermectin (IVM) concentrations suppress in vitro SARS-CoV-2 replication. Nasal IVM spray (NIVM spray) administration may contribute to attaining high drug concentrations in nasopharyngeal (NP) tissue, a primary site of virus entrance/replication. The safety and pharmacokinetic performance of a new NIVM spray formulation in a piglet model were assessed. Crossbred piglets (10/12 kg) were treated with either one or two (12 h apart) doses of N IVM spray (2 mg, 1 puff/nostril) or orally (0.2 mg/kg). The overall safety of NIVM-spray was assessed (clinical, haematological, serum biochemical determinations), and histopathology evaluation of the application site tissues performed. The IVM concentration profiles measured in plasma and respiratory tract tissues (nasopharynx and lungs) after the nasal spray treatment (one and two applications) were compared with those achieved after the oral administration. Animals tolerated well the novel NIVM spray formulation. No local/systemic adverse events were observed. After nasal administration, the highest IVM concentrations were measured in NP and lung tissues. Significant increases in IVM concentration profiles in both NPtissue and lungs were observed after the 2 dose nasal administrations. The nasal/oral IVM concentration ratios in NP and lung tissues (at 6 h postdose) markedely increased by repeating the spray application. The fast attainment of high and persistent IVM concentrations in NP tissue is the main advantage of the nasal over the oral route. These original results are encouraging to support the undertaking of further clinical trials to evaluate the safety/efficacy of the nasal IVM spray application in the treatment and/or prevention of COVID-19. [**note: this is from Argentina and these researchers have come up with a nasal spray formulation of ivermectin. While this compound has demonstrated *in vitro* activity I have seen no published results of any of the clinical trials.**] https://www.biorxiv.org/content/10.1101/2020.10.23.352831v1
- K777 is a di-peptide analog that contains an electrophilic vinyl-sulfone moiety and is a potent, covalent inactivator of cathepsins. Vero E6, HeLa/ACE2, Caco-2, A549/ACE2, and Calu-3, cells were exposed to SARS-CoV-2, and then treated with K777. K777 reduced viral infectivity with EC50 values of inhibition of viral infection of: 74 nM for Vero E6, <80 nM for A549/ACE2, and 4 nM for HeLa/ACE2 cells. In contrast, Calu-3 and Caco-2 cells had EC50 values in the low micromolar range. No toxicity of K777 was observed for any of the host cells at 10-100 µM inhibitor. K777 did not inhibit activity of the papain-like cysteine protease and 3CL cysteine protease, encoded by SARS-CoV-2 at concentrations of ≤ 100 µM. These results suggested that K777 exerts its potent anti-viral activity by inactivation of mammalian cysteine proteases which

are essential to viral infectivity. Using a propargyl derivative of K777 as an activity-based probe, K777 selectively targeted cathepsin B and cathepsin L in Vero E6 cells. However only cathepsin L cleaved the SARS-CoV-2 spike protein and K777 blocked this proteolysis. The site of spike protein cleavage by cathepsin L was in the S1 domain of SARS-CoV-2 , differing from the cleavage site observed in the SARS CoV-1 spike protein. These data support the hypothesis that the antiviral activity of K777 is mediated through inhibition of the activity of host cathepsin L and subsequent loss of viral spike protein processing. [**note: this is from UC San Diego. The experimental drug, K777, has been around for quite a while according to the paper. Part of the funding for this comes from Selva Therapeutics who have a drug ready for clinical trials but it is unclear whether it is this or a derivative. It is a drug that can be given orally or by infusion.**] https://www.biorxiv.org/content/10.1101/2020.10.23.347534v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Autophagy modulators have emerged as potential therapeutic candidates against SARS-CoV-2 but recent clinical setbacks underline the urgent need for better understanding the mechanism of viral subversion of autophagy. Using murine hepatitis virus-A59 (MHV-A59) as a model betacoronavirus, time-course infections revealed a significant loss in the protein level of ULK1, a canonical autophagy regulating serine-threonine kinase, and the concomitant appearance of a possible cleavage fragment. To investigate whether virus-encoded proteases target this protein, we conducted in vitro and cellular cleavage assays and identified ULK1 as a novel bona fide substrate of SARS-CoV-2 papain-like protease (PL^{pro}). Mutagenesis studies discovered that ULK1 is cleaved at a conserved PL^{pro} recognition sequence (LGGG) after G499, separating its N-terminal kinase domain from the C-terminal substrate recognition region. *Consistent with this, over-expression of SARS-CoV-2 PL^{pro} is sufficient to impair starvation-induced canonical autophagy and disrupt formation of ULK1-ATG13 complex. Finally, we demonstrated a dual role for ULK1 in MHV-A59 replication, serving a pro-viral functions during early replication that is inactivated at late stages of infection. In conclusion, our study identified a new mechanism by which PL^{pro} of betacoronaviruses induces viral pathogenesis by targeting cellular autophagic pathway*. [**note: here is another mode of action of the viral protease that may be clinically important.**] https://www.biorxiv.org/content/10.1101/2020.10.23.353219v1
- SARS-CoV-2, the causative agent of COVID-19, has an RNA genome, which is, overall, closely related to the bat coronavirus sequence RaTG13. However, the ACE2-binding domain of this virus is more similar to a coronavirus isolated from pangolin. In addition to this unique feature, the genome of SARS-CoV-2 (and its closely related coronaviruses) has a low CpG content. This has been postulated to be signature of an evolutionary pressure exerted by the host antiviral protein ZAP. Here, we analyzed the sequences of a wide range of viruses using both alignment-based and alignment free approaches to investigate the origin of SARS-CoV-2 genome. *Our analyses revealed a high level of similarity between the 5UTR of SARS-CoV-2 and that of a Guangdong pangolin coronavirus. These data suggest that not only ACE2, but also the 5UTR of SARS-CoV-2 likely has a pangolin coronavirus origin. Additionally, we performed a detailed analysis of viral genome compositions as well as expression and RNA binding data of ZAP to show that the low CpG abundance in SARS-CoV-2 is not related to an evolutionary pressure from ZAP*. [**note: here is a comparative study of SARS-CoV-2 and a similar virus from pangolins.**] https://www.biorxiv.org/content/10.1101/2020.10.23.351353v1

- We herein report a computational study on the implications of SARS-CoV-2 RBD mutations and the Angiotensin Converting Enzyme 2 (ACE2) receptor genetic variations on the stability of the virus-host association. In silico analysis of the complex between the virus mutated forms and ACE2 isoform 1 showed that out of 351 RBD point mutations, 83% destabilizes the complex, while 17% have mild stabilizing effect. Study of the complex SARS-CoV-2 Wuhan strain RBD region /ACE2 isoform 1, 6LZG PDB 3D model revealed 18 contact residues. Interestingly, mutations occurring in 15 out of these residues show variations in the patterns of polar and hydrophobic interactions as compared to the original complex. Similarly, comparison of the effect on the complex stability of different ACE2 variants showed that the pattern of molecular interactions and the virus-receptor complex stability varies also according to ACE2 polymorphism. This could explain the large inter-individual variation of disease susceptibility and/or severity. *The observation of a high variability in the interactions patterns highlights the complexity of the molecular interplay between SARS-CoV-2 and the ACE2 receptor. We infer that it is important to consider both ACE2 genetic variants and SARS-CoV-2 RBD mutations to assess the stability of the virus-receptor association and evaluate the infectivity of circulating SARS-CoV-2. These findings point toward the importance of individuals genetic typing of the circulating viral form as well as the ACE2 receptor*. This will offer a good molecular ground to adjust the mitigation efforts for a better control of the virus spreading. [**note: this is a study of the impact of mutation and genetic variability of the binding between the virus and the ACE2 receptor. Genetic variants are likely to play a role in infectivity.**]
https://www.biorxiv.org/content/10.1101/2020.10.23.352344v1
- Exacerbated pro-inflammatory immune response contributes to COVID-19 pathology. However, despite the mounting evidence about SARS-CoV-2 infecting the human gut, little is known about the antiviral programs triggered in this organ. To address this gap, we performed single-cell transcriptomics of SARS-CoV-2-infected intestinal organoids. *We identified a subpopulation of enterocytes as the prime target of SARS-CoV-2 and, interestingly, found the lack of positive correlation between susceptibility to infection and the expression of ACE2. Infected cells activated strong proinflammatory programs and produced interferon, while expression of interferon-stimulated genes was limited to bystander cells due to SARS-CoV-2 suppressing the autocrine action of interferon. These findings reveal that SARS-CoV-2 curtails the immune response and highlights the gut as a proinflammatory reservoir that should be considered to fully understand SARS-CoV-2 pathogenesis*. [**note: from the European Molecular Biology Lab, more information on the immune response, this time in the human gut.**]
https://www.biorxiv.org/content/10.1101/2020.10.21.348854v1

DIAGNOSTIC DEVELOPMENT

- Nothing today.