Summary of Major Literature Related to COVID-19 (Oct 27-Nov 16)

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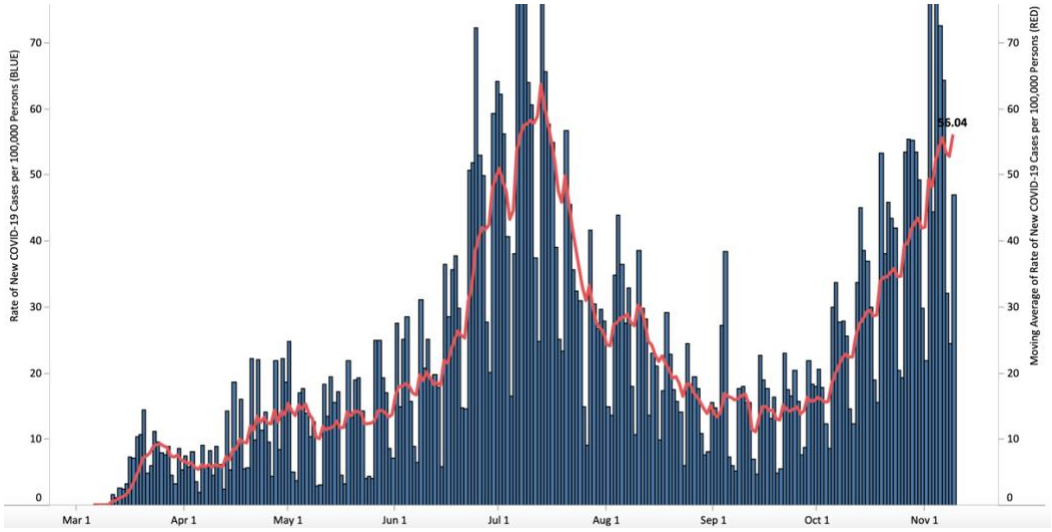
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Daily new cases per 100,000 population

Tennessee

Davidson county



As of November 15, in TN

- Total cases = 310,937
- Active cases = 36,953
- Current hospitalizations = 1,785
- Total deaths = 3,893
- Top counties:
  - Shelby = 42,660
  - Davidson = 39,843 (active cases = 3,231; ICU availability = 13%; test % positive = 8.6%)
- Active cases in Davidson co. and TN continue to increase since early Oct
- Demographics:

Groups	Cases	Deaths
By sex		
Female	162,289	1,744
Male	146,236	2,147
By race/ethnicity		
White	178,022	2,755
Black	47,680	868
Hispanic	29,772	170
Asian	2,633	30
Other	32,304	150
By age (average: 40 years)		
0–10	15,257	4
11–20	41,369	1
21–30	60,834	25
31–40	49,475	54
41–50	46,055	139
51–60	41,637	367
61–70	29,102	753
71–80	17,360	1,175
80+	9,408	1,374

November 16, 2020: **Promising Interim Results from Clinical Trial of NIH-Moderna COVID-19 Vaccine**

Interim analysis of Phase 3 vaccine efficacy trial (COVE) of the investigational COVID-19 vaccine known as mRNA-1273 suggests that the vaccine is safe and effective at preventing symptomatic COVID-19 in adults, with a 94.5% efficacy rate. In the interim analysis of 95 cases of symptomatic COVID-19 among volunteers, 90 occurred in the placebo group and 5 occurred in the vaccinated group. There were 11 cases of severe COVID-19 out of the 95, all of which occurred in the placebo group. The trial includes >30,000 participants, 37% of whom are from racial and ethnic minorities.

See also: **VACCINE CANDIDATE TRACKER**

Developed by the Vaccine Centre at the London School of Hygiene & Tropical Medicine to follow candidates as they progress through the development pipeline.

EPIDEMIOLOGY

Seroprevalence/Infection fatality rate (IFR)

1. **Age-specific mortality and immunity patterns of SARS-CoV-2.** O'Driscoll et al. Nature. 02 Nov 2020.

- Using a model framework to integrate age-specific COVID-19 death data from 45 countries and the results of 22 seroprevalence studies, the authors estimated IFRs by age and sex and derived the proportion of the population infected in each country
- IFR is lowest among 5-9 years old but increases with age among individuals older than 30 years following a log-linear pattern
- Age distribution of deaths in younger age groups (<65 years) is very consistent across different settings but varies substantially in older individuals across countries
- IFR estimates are highest for countries with older populations, particularly in nursing homes
- Authors estimate that approximately 5% of the populations studied had been infected by September 1, with higher transmission likely in several Latin American countries

2. **Infection fatality rate of COVID-19 inferred from seroprevalence data.** Ioannidis. Bulletin of the World Health Organization. 14 Oct 2020.

- Analysis of 61 published studies with a sample size >500 and 8 preliminary national estimates
- Seroprevalence estimates ranged from 0.02% to 53.40%; IFRs ranged from 0.00% to 1.63%
- Across 51 locations, the median COVID-19 IFR was 0.27%
    - the rate was 0.09% in locations with COVID-19 population mortality rates less than the global average (< 118 deaths/million), 0.20% in locations with 118–500 COVID-19 deaths/million people and 0.57% in locations with > 500 COVID-19 deaths/million people
    - in people < 70 years, IFR ranged from 0.00% to 0.31% with median of 0.05%
- Limitation: Unknown representativeness of seroprevalence studies

Implications relevant to both studies:

- Population age-structures, heterogeneous burdens of nursing homes, and variations in population mixing of high and low risk groups among infected and deceased patients contribute to heterogeneity between countries in IFR
- IFRs are lower than estimates that were made earlier in the pandemic, which were likely influenced by high mortality due to overwhelmed hospitals and unfamiliarity with COVID-19 management

Antibody response

3. **Robust neutralizing antibodies to SARS-CoV-2 infection persist for months.** Wajnberg et al. Science. 28 Oct 2020.

- SARS-CoV-2 spike protein is the main target for neutralizing antibodies
- Study of 30,082 individuals who recovered from mild to moderate COVID-19 and screened positive for SARS-CoV-2 spike antibodies (detectible antibodies to the spike protein at a titer of 1:80 or higher) at Mount Sinai Health System in New York City using high sensitivity and specificity ELISA
- 93% experienced moderate to high IgG antibody responses against the viral spike protein (titers 1:320 or higher of anti-spike antibodies), which correlated significantly with neutralization of authentic SARS-CoV-2 virus
    - 90-100% of sera in the >1:320 range had neutralizing activity

- To assess the medium-range stability of serum antibody titers against the spike protein, a series of repeat measurements were performed in a small subset (n=121) at, on average, day 52 and day 82 post-symptom onset
    - Antibody titers were relatively stable over a period of at least 3 months and modestly decline at the 5-month time point
    - However, among some mild COVID-19 cases, very low initial titers might drop to undetectable levels over time
    - Good correlation between neutralization and ELISA titers was still observed on day 148
- Limitation: Potential bias due to missing individuals who had been infected with SARS-CoV-2 and did not produce antibodies, but based on prior smaller studies this percentage is expected to be low (<5%); no data on antibody response among asymptomatic COVID-19 patients
- Implications: More than 90% of seroconverters who have recovered from mild to moderate COVID-19 make detectible neutralizing antibody responses and have relatively stable titers for several months after infection; it is unknown whether these antibody responses protect from reinfection, but they may decrease the odds of reinfection or attenuate disease in the case of reinfection

4. **Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans.** Seow et al. Nature Microbiology. 26 Oct 2020**.**

- Antibody responses to SARS-CoV-2 infection can be detected in most infected individuals 10–15 d after the onset of the symptoms. However, it is unknown how long antibody responses will be maintained.
- Researchers enrolled 65 individuals and collected sequential serum samples up to 94 days post onset of symptoms
- The study demonstrates a typical antibody response to SARS-CoV-2, including IgA, IgG and IgM, can be detected in >95% infected individuals when sampled beyond 8 days after viral infection
    - Peak response was detected 3-4 weeks post-infection, and then waned
- The kinetics of the neutralizing antibody response is typical of an acute viral infection, with declining antibody titers observed after an initial peak
    - The magnitude of this peak is dependent on disease severity.
    - For those who develop a low neutralizing antibody response (serum dilution that inhibits 50% infection (ID50): 100–300), titers can return to baseline over a relatively short period, whereas those who develop a robust neutralizing antibody response maintain titers >1,000 despite the initial decline
- Implications: Further studies at extended timepoints are required to determine the longevity of the neutralizing antibody response as well as the neutralizing antibody threshold for protection from reinfection and/or disease

Transmission

5. **Transmission of SARS-COV-2 Infections in Households — Tennessee and Wisconsin, April–September 2020.** Grijalva et al (**VUMC authors**). MMWR. 69(44);1631–1634. 06 Nov 2020**.**

- Objective of the study was to assess household transmission. A case-ascertained study was conducted in Nashville, Tennessee, and Marshfield, Wisconsin, commencing in April 2020
- Index patients were defined as the first household members with COVID-19–compatible symptoms who received a positive SARS-CoV-2 RT-PCR test result, and who lived with at least one other household member
    - Index patients and household completed symptom diaries and obtained self-collected specimens, nasal swabs only or nasal swabs and saliva samples, daily for 14 days
    - Specimens from the first 7 days were tested for SARS-CoV-2 using CDC RT-PCR protocols

- Enrolled 101 index patients and 191 household contacts
    - All 191 household contacts reported no symptoms on day of index patient's illness onset
    - Median index patient age was 32 years (range 4–76 years)
    - Among index patients, 75 (74%) were non-Hispanic White, eight (8%) were non-Hispanic persons of other races, and 18 (18%) were Hispanic or Latino
- Overall secondary infection rate for household contacts was 53% with 102 household contacts having SAR-CoV-2 detected in specimens during follow up
    - Secondary infection rate from index patients aged <12 years (n=5) was 53% (95% CI = 31%–74%) and from index patients aged 12–17 years (n=9) was 38% (95% CI = 23%–56%)
- ~75% of secondary infections were identified within 5 days of index patient's illness onset and substantial transmission occurred regardless of index patient being adult or child
    - 67% (68 of 102) of infected household members reported symptoms, which began a median of 4 days (IQR = 3–5) after the index patient's illness onset
    - 40% (41 of 102) of infected household members reported symptoms at the time SARS-CoV-2 was first detected by RT-PCR
- Implications: Household transmission of SARS-CoV-2 is common and can occur rapidly after the index patient's illness onset. Individuals should self-isolate immediately at the onset of COVID-like symptoms, at the time of testing as a result of a high-risk exposure, or at the time of a positive test result, whichever comes first. Concurrent to isolation, all members of the household should wear a mask when in shared spaces in the household
- Limitations: Possible for misclassification of true index patient if household members were asymptomatic; secondary infection rates could have occurred from outside household contact; families may not be representative of general US population

See also: SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study. Ng et al. Lancet Infect Dis. 02 Nov 2020.

- Study in Singapore of 7770 close contacts linked to 1114 PCR-confirmed cases from Jan 23-April 3
    - All patients with COVID-19 in Singapore received inpatient treatment, with access restricted to health-care staff
    - All close contacts were quarantined for 14 days with thrice-daily symptom monitoring via telephone. Symptomatic contacts underwent PCR testing for SARS-CoV-2
- Secondary clinical attack rate was 5.9% for 1779 household contacts, 1.3% for both work contacts and social contacts
- Among both household and non-household close contacts, close physical proximity and increased duration of verbal interaction were risk factors for SARS-CoV-2 transmission
- Implication: A comprehensive approach to COVID-19 control and contact tracing contributes to low secondary attack rate among household and non-household contacts

Viral load

6. **Comparison of upper respiratory viral load distributions in asymptomatic and symptomatic children diagnosed with SARS-CoV-2 infection in pediatric hospital testing programs.** Kociolek et al. J Clin Microbiol. 22 Oct 2020.

- Collaborative study of viral load in upper respiratory samples of asymptomatic (n=339) and symptomatic (n=478) children infected with SARS-CoV-2 at nine children's hospitals in the US and Canada at different stages of the pandemic
    - Primary reasons for testing among asymptomatic were contact tracing/community surveillance, pre-op or hospital admission screening

    - Each asymptomatic patient was matched to two symptomatic patients by age bracket (0-4y, 5-9y, 10-13y, 14-17y) and date of testing
- Ct values for each assay were adjusted by centering each value around the institutional symptomatic median, and viral load estimate (copies/mL sample) was provided for each Ct value
- The median adjusted Ct value in asymptomatic children was 8.6 (IQR 2.5 to 12.2) compared to -1.7 (IQR-6.0 to 4.8) in symptomatic children ($p< 0.0001$); similarly, median estimated viral loads were lower in asymptomatic children (2.0×10^3 copies/mL) than symptomatic children (1.3×10^7 copies/mL; $p<0.0001$)
    - Differences in viral burden were consistent across all age brackets and institutions
- Asymptomatic children with diabetes (OR 6.5, $p = 0.01$), recent contact with a COVID-19 case (OR 2.3, $p = 0.02$), and testing for surveillance (OR 2.7, $p = 0.005$) had higher estimated risk of having a Ct value in the lowest quartile than children without
- In the asymptomatic group, children who were pre-symptomatic children (developed symptoms within 5 days following the test) had non-significantly higher median viral loads than non-pre-symptomatic children
- Implications: Asymptomatic children have significantly lower levels of the virus in the nasopharynx/oropharynx than symptomatic children but overlap between the two groups was noted for all age brackets. Other risk factors, including diabetes or recent infection, may contribute to high viral load in some asymptomatic children
- Limitation: Data may not represent the distribution of viral load in recently infected asymptomatic children or at peak viral load; unknown whether low viral loads in children correlate with ability to recover virus in culture, and lower viral loads in asymptomatic children do not themselves provide evidence related to potential for transmission

GENETICS

Host susceptibility

7. **Initial whole-genome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility.** Wang et al. Cell Discovery. 10 Nov 2020.

- Whole genome sequencing (46x) study of 332 hospitalized COVID-19 patients in Shenzhen City, China, categorized by levels of disease severity: asymptomatic, mild, moderate, severe, and critically ill
- A recurrent loss of function variant in gene *GOLGA3* was identified among the critically ill patients and a recurrent loss of function 1-bp insertion in gene *DPP7* among the asymptomatic patients
    - Both genes related to the host immune response to the viral infection
- Previously identified missense variant rs12329760 in *TMPRSS2* was less frequent among the critical patients compared to other patients and the general population
    - This variant has been predicted to decrease TMPRSS2 protein stability and ACE2 binding
- The genome-wide association analysis identified a gene locus associated with severity that was located in *TEMEM189–UBE2V1*, known to function in the IL-1 signaling pathway
- Limitations: Small study with low statistical power and lack of validation, thus cautious interpretation is required
- Implications: Host genetic factors may play a role in determining host responses to SARS-CoV-2 infection

Viral infectivity

8. **SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo.** Hou et al. Science. 12 Nov 2020.

- The spike D614G substitution (in the spike protein) is the most prevalent in SARS-CoV-2 strains

- An isogenic SARS-CoV-2 variant was engineered containing only the D614G substitution and a nanoluciferease gene for tracking; its impact on viral pathogenesis was assessed
- While there were only mild or inconsistent differences in infectivity of cell lines, the variant exhibits more efficient infection, replication, and competitive fitness in primary nasal epithelium but maintains similar morphology, spike cleavage pattern, and sensitivity to antibodies compared with the wild-type virus
- Infection of human angiotensin-converting enzyme 2 (ACE2) transgenic mice and Syrian hamsters with both wild-type and engineered viruses resulted in similar viral titers in respiratory tissues and pulmonary disease
- Using a hamster model of transmissibility, the D614G variant transmitted significantly faster that the WT virus (5 of 8 variants compared to 0 of 8 WT transmitted by day 2); D614G variant also displayed increased competitive fitness over the wild-type virus in an in vivo assay
- Limitation: No mechanistic insight as to why this variant may transmit better; unclear if these findings will translate to human infections (and virus genotype is not known in most infections)
- Implications: These data show that the D614G substitution enhances SARS-CoV-2 infectivity, competitive fitness, and transmission in primary human cells and animal models

TREATMENT

9. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19. A Randomized Clinical Trial. Lenze et al. JAMA. 12 Nov 2020**.**

- Preliminary double-blind, randomized, fully remote (contactless) clinical trial of 152 adult outpatients with confirmed COVID-19 and symptom onset within 7 days, randomly assigned to receive 100 mg of fluvoxamine (n = 80) or placebo (n = 72) 3 times daily for 15 days
    - Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and σ-1 receptor (S1R) agonist
    - Mean [SD] age, 46 [13] years; 72% women; 25% Black
- Primary outcome was clinical deterioration within 15 days of randomization defined by meeting both criteria of (1) shortness of breath or hospitalization for shortness of breath or pneumonia; and (2) oxygen saturation less than 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92% or greater
- Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (absolute difference, 8.7% [95% CI, 1.8%-16.4%] from survival analysis; log-rank *P* = .009)
    - 4/6 patients were hospitalized for COVID-19 illness, 1 patient required mechanical ventilation, no patients died
- The fluvoxamine group had 12 adverse events (1 serious), whereas the placebo group had 18 (6 serious) adverse events
- Implication: Fluvoxamine, given as early treatment in individuals with mild COVID-19 illness, may prevent clinical deterioration
- Limitation: Small study, requires confirmation in larger trial with more definitive outcomes measures

HUMAN IMMUNE RESPONSE

10. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Zou et al. Science Translational Medicine. 2 Nov 2020**.**

- Cross-sectional examination of phospholipid autoantibodies in hospitalized COVID-19 patients and their relationship to thrombosis and occlusion of vasculature

- Anti-phospholipid autoantibodies were found in 52% of serum samples assayed; autoantibodies surveyed included those directed against cardiolipin, beta2 glycoprotein, and phosphatidylserine/ prothrombin
- Anti-phospholipid autoantibodies derived from COVID-19 patients showed similar pathologic activity to those derived from patients with the autoimmune disease, anti-phospholipid syndrome; drove NETosis (neutrophil extracellular trap (NET) release)
- Increased anti-phospholipid autoantibody titers correlated with increased platelet counts, respiratory disease severity, and lower eGFR.
- IgG purified from COVID-19 sera accelerated thrombosis in mouse models.
- Dipyridamole mitigated NET release as a COVID-19 therapy is currently in clinical trial
- Limitations: Association between circulating anti-phospholipid antibodies and large artery/vein thrombosis was not observed. Given the focus on hospitalized patients, it is unclear whether findings extend to individuals with mild to moderate COVID-19 disease
- Implications: Patients who are anti-phospholipid antibody positive may benefit from strategies effective in managing anti-phospholipid syndrome, such as heparin, corticosteroids, and plasmapheresis

11. Versatile and multivalent nanobodies efficiently neutralize SARS-CoV-2. Xiang et al. Science. 5 Nov 2020**.**

- SARS-CoV-2 neutralizing nanobodies (Nbs) were produced by immunizing a llama with recombinant receptor binding domain of spike (RBD) and separating the single chain V_HH antibodies from the IgGs; high affinity binding and neutralizing ability was confirmed with pseudotyped virus
- A proteomics strategy was used to screen 1000s of high-affinity V_HH Nbs and 109 diverse sequences were selected for expression in *E.coli;* ultimately 49 Nb were selected for study due to high- affinity binding and high solubility; neutralization assays further identified the three most potent Nbs (14 had neutralizing abilities in the PRNT50 assay)
- Nbs 89, 20, and 21 were shown to have physicochemical properties which are consistent with therapeutic applications including thermostability and no formation of aggregations
- Cross-linking models identified five epitopes corresponding to Nbs 20, 93, 34, 95, and 105 (two overlap with the hACE2 binding site)
- Structural analysis and modeling were performed for some of these Nbs; differences between Nb20 and Nb21 (epitope I) binding of RBD suggest that their interfaces overlap and likely the CDR1 and CDR3 would clash with hACE2 blocking binding; further Nb20/21 may lock the RBD in its "down" confirmation; Epitope II binding Nb93 binds RBD in its "up" confirmation but may still block the hACE2 biding site; Epitope II and IV only bind when 2 or 3 RBDs are in their "up" confirmation
- Homodimeric and heterodimeric multi-valent constructs were created with these Nb and frequently increased potency while preserving solubility and thermostability
- Limitations: No in vivo assessment of efficacy (no animal model and not to clinical trials yet)
- Implications: Multivalent constructs that bind simultaneously a variety of epitopes with potentially different neutralization mechanisms are highly potent and could efficiently block virus mutational escape

12. Preexisting and de novo humoral immunity to SARS-CoV-2 in humans. Ng et al. Science. 06 Nov 2020**.**

- A flow-cytometry based assay was used to identify SARS-CoV-2 binding antibodies using HEK293T cells expressing the SARS-CoV2 Spike protein; the assay's validity was shown using COVID-19 convalescent sera; further, a combination of S1 and S2 subunits could reduce the staining in competition with the cells.

- A small proportion of SARS-CoV-2 uninfected patients had IgG binding to the SARS-CoV2-S protein (but no IgM or IgA); recombinant soluble S2 subunit could abolish staining with the uninfected patient sera
- SARS-CoV2 S reactive IgG were detected by flow cytometry in 5 of 34 SARS-CoV2 uninfected patients who had PCR confirmed human coronavirus infections (HCoV); 1 of 31 persons without recent HCoV infection also had reactive IgG.
- Several cohorts of SARS-CoV-2 uninfected donors were screened; in pregnant women 5/50, in 3/101 donors from May 2019, 1/13 donors with known HCoV infections, 21/48 in healthy children 1-16 yo, and 1/43 in an additional cohort of 17-25 yo showed evidence for SARS-COV-2 S reactive IgG; prevalence of S reactive IgG peaked between 6 and 16 years and was significantly higher than in adults
- Sera from SARS-CoV-2-uninfected donors with SARS-CoV-2 S-reactive antibodies inhibited SARS-CoV-2 entry into HEK293T cells & neutralized pseudotypes, and most neutralized SARS-CoV2 infection of Vero E6 cells (sera from SARS-CoV-2-uninfected patients without cross-reactive antibodies exhibited no neutralizing activity in these assays)
- The cross-reactive epitopes were mapped and reactivity with one or more HCoV was detectable in all sera; the conserved epitopes are mostly in the S2 subunit which is most conserved.
- Limitations: Unclear if these cross-reactive Ab may also induce antibody mediate enhancement; No evidence (here or elsewhere) that pre-existing antibodies impact natural COVID-19 disease course.
- Implications: We need a better understanding of the impact of preexisting HCoV-elicited immunity on natural SARS-CoV-2 infections

THERAPEUTIC/VACCINE DEVELOPMENT

13. **Identification of SARS-CoV-2 Inhibitors using Lung and Colonic Organoids.** Han et al. Nature. 28 Oct 2020**.**

- Human lung organoids (hPSC-LOs) were generated from differentiated human pluripotent stem cells
- qRT-PCR and RNA-seq profiling demonstrated expression of alveolar type II (AT2) cell markers, single cell transcriptomic profiles of hPSC-LOs identified AT2-like cells, which were enriched for adult human lung AT2 cell markers
- SARS-CoV-2 readily infected hPSC-LOs. Gene set enrichment analysis (GSEA) of infected hPSC-LOs demonstrated over-represented pathway networks that were reflective of what is seen in lung autopsy tissue from COVID-19 patients. These pathways included rheumatoid arthritis, TNF signaling, IL-17 signaling, and cytokine-cytokine receptor interaction.
- hPSC-LOs were treated with a library of FDA-approved drugs. Imatinib, mycophenolic acid (MPA), quinacrine dihydrochloride (QNHC), and chloroquine were found to inhibit infection with SARS-CoV-2 in a dose dependent manner, independent of cytotoxicity. These findings were corroborated in humanized mice carrying hPSC-derived lung xenografts, treated with imatinib mesylate, MPA or QNHC prior to intra-xenograft inoculation with SARS-CoV-2
- Human colonic organoids (hPSC-COs) contained all the major cells types, expressed ACE2, and were readily infected with SARS-CoV-2. GSEA revealed over-represented pathway networks in hPSC-Cos that were comparable to those seen in SARS-CoV-2 infected hPSC-LOs and lung autopsy tissue from COVID-19 patients
- Drug treatment of hPSC-COs with imatinib, MPA, or QNHC prior to infection significantly reduced viral infection
- Limitations: The cellular responses being assessed in the organoid systems do not fully represent the physiological/pathological responses seen in humans. Drugs were only administered prior to infection.
- Implications: Human pluripotent stem cell-derived lung and colonic organoids provide high throughput and more physiologically relevant experimental models compared to traditional transformed cell lines to more efficiently screen and identify candidate therapies for COVID-19

14. **Elicitation of Potent Neutralizing Antibody Responses by Designed Protein Nanoparticle Vaccines for SARS-CoV-2.** Walls et al. Cell. 30 Oct 2020.

- Nanoparticle vaccine candidates were designed to display 60 SARS-CoV-2 Spike receptor binding domains; the RBD- nanoparticles are high yield and highly stable
- RBD-I53-50 nanoparticles elicited potent neutralizing Ab responses in BALB/c and human immune repertoire mice
    - In Balb/C mice (groups of 10 mice, 2 possible doses, 2 immunizations at 0 and 3 weeks): Nanoparticles elicited S-specific Ab responses with GMT ranging from 8×10^2 and 1×10^4 3 weeks after the first dose; increased ~2-3 logs with the second dose; The nanoparticles induced Ab responses 1-2x stronger than the 5 µg doses of Spike-2P trimer (and the monomeric RBD did not elicit detectable Ag-specific Abs after two immunizations)
    - Serum neutralizing Abs were present after the first dose of nanoparticles and increased with the second dose; monomeric RBD or S-2P trimer did not elicit neutralizing Abs after a single immunization (only the higher dose of S-2P elicited neutralizing Ab after the 2nd dose)
    - S-specific Abs matched or exceeded most samples from a panel of 30 COVID-19 human convalescent sera (HCS)
    - In Darwin mice (engineered to express fully human kappa light chain Abs) (groups of 5, 2 doses and 2 immunizations at 0 and 3 weeks): nanoparticles elicited Ab responses post-prime (EC50 2×10^3–$1x10^4$) that were substantially boosted by a second immunization at week 3 (~2 logs). In this animal model, the S-2P trimer (at the higher dose) elicited levels of S-specific Abs comparable to the RBD nanoparticles after each immunization.
    - RBD-Nanoparticles in Darwin mice elicited neutralizing Ab titers comparable to HCS after a single immunization; 5 µg of the S-2P trimer did not elicit detectable levels of neutralizing Abs despite eliciting total S-specific Ab
- Mice were immunized with either adjuvant alone, monomeric RBD, S-2P trimer, or RBD-8Gs or RBD-12GS-I53-50 nanoparticles; both nanoparticle formulations provided protection from detectable mouse adapted SARS-CoV-2 replication in lung and nasal turbinates (no protection from other immunizations)
- RBD nanoparticle immunization resulted in expansion of RBD-specific B cells and germinal center precursors and B cells; magnitude of both binding and neutralization titers at 20-24 weeks were similar to levels two weeks post-boost for all nanoparticle groups.
- Pigtail macaques were immunized with the RBD-12GS-I53-50 nanoparticles at 0 and 4 weeks and Abs targeting several non-overlapping epitopes were detected (should not lead to the emergence or selection of escape mutants)
- Implications: Nanoparticle vaccines may provide a robust antigen presentation, elicit potent Ab responses and should be considered due to ability to scale their production for vaccine distribution.