Summary of Major Literature Related to COVID-19 (Oct 13-26)

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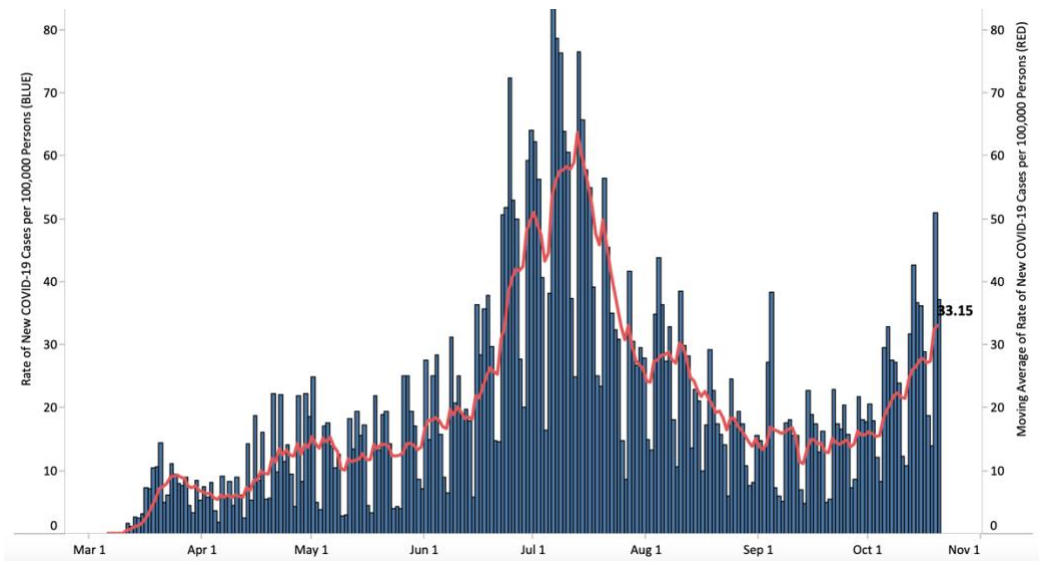
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Daily new cases per 100,000 population

Tennessee

Davidson county



As of October 26, in TN

- Total cases = 249,866
- Active cases = 27,473
- Current hospitalizations = 1,098
- Total deaths = 3,163
- Top counties:
  - Shelby = 36,685
  - Davidson = 33,699 (active cases = 2,490 ICU availability = 13%)
- Active cases in Davidson co. and TN continue to increase since early Oct.
- Demographics:

Groups	Cases	%
By sex		
Female	129,127	51.7%
Male	118,752	47.5%
By race/ethnicity		
White	141,495	56.6%
Black	41,529	16.6%
Hispanic	27,415	11.0%
Asian	2,167	0.9%
Other	37,260	14.9%
By age (average: 40 years)		
0–10	12,195	4.9%
11–20	33,110	13.3%
21–30	50,089	20.0%
31–40	40,272	16.1%
41–50	37,020	14.8%
51–60	33,073	13.2%
61–70	22,826	9.1%
71–80	13,534	5.4%
80+	7,393	3.0%

EPIDEMIOLOGY

COVID-19 mortality/excess mortality

1. COVID-19 and Excess All-Cause Mortality in the US and 18 Comparison Countries. Bilinski and Emmanuel. JAMA. October 12.

- For the US and 18 other countries: calculated COVID-19 per capita mortality rates and all-cause mortality per capita to estimate excess US deaths compared to other countries
- Used three different time points: Since the start of the pandemic, since May 10, 2020, and since June 7, 2020; this is an indirect comparison of temporal differences in national approaches to pandemic
- US has same overall mortality as other high mortality countries (UK, Belgium, Spain, Italy, Sweden)

- However, mortality decreased substantially over time in all countries such that the US far exceeds mortality in all other countries (22% to 61% higher depending on timepoint)
    - This equates to 44,210 to 120,625 excess deaths. Similar pattern for excess deaths from any cause
- Limitations: Mortality data were incomplete; analysis could not account for higher prevalence of comorbidities in US; mortality rates have started to increase in other countries and could not evaluate
- Implication: The US approach to the pandemic has been less successful at preserving lives than the approaches in other countries

2. **Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity — United States, January 26–October 3, 2020.** Rossen et al. MMWR. October 23**.**

- This study examined excess deaths, or the difference between the weekly number of deaths occurring in 2020 and the average number occurring in the same week during 2015–2019
- Excess deaths have occurred every week since March
- Overall, an estimated 299,028 excess deaths have occurred in the US from January 26 to October 3, with two-thirds of these attributed to COVID-19 and the remaining third to other causes
- By age: highest number (94,646) of excess deaths relative to past years was among adults aged 75-84 years, but average percentage change in deaths was largest for adults aged 25–44 years (26.5%)
- By race/ethnicity: average percentage increase was highest for Hispanic or Latino persons (53.6%) and lowest for White persons (11.9%), 28.9% for American Indian/Alaska Native persons, 32.9% for Black persons, and 36.6% for Asian persons
- Limitation: Potential misclassification of cause of death
- Implications: Reported numbers of deaths from COVID-19 may underestimate the total impact of the pandemic on mortality, due to factors such as availability or use of testing and accuracy or completeness of cause of death reporting

3. **Mortality among Adults Ages 25-44 in the United States During the COVID-19 Pandemic.** Faust et al. medRxiv preprint. October 25.

- Observational cohort study examining all-cause mortality among adults age 25-44y using public data from the National Center for Health Statistics and CDC Wonder
- 74,027 all-cause deaths occurred among persons ages 25-44 years during the period from March 1-July 31, 2020, 14,155 more than the same period in 2019, representing a 23% relative increase (incident rate ratio 1.23; 95% CI 1.21-1.24)
    - 28.7% (4,055/14,155) of the excess deaths were attributed to COVID-19
- In Health and Human Services (HHS) Region 2 (New York, New Jersey), Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, Texas), and 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
- Limitation: Reporting lags; possible under-detection of COVID-19 in this age group
- Implication: COVID-19 mortality among young adults aged 25-44 is not negligible

4. **Trends in COVID-19 Risk-Adjusted Mortality Rates.** Horwitz et al. J Hosp Med. October 23**.**

- Electronic health record-based analysis of in-hospital mortality or discharge to hospice among all 5,118 adults hospitalized COVID-19 patients in one hospital system in NYC from March-August
    - Median age and proportion male or with any comorbidity decreased over time
    - 53% of the hospitalizations occurred from late March to mid-April

- Adjusted mortality dropped each month, from 25.6% in March to 7.6% in August, adjusted for demographic and clinical factors, including comorbidities, admission vital signs, and laboratory results
    - Declines observed across all age groups
- Average probability of death was 18.2 percentage points lower in August than in March
- Implications: Improved mortality among COVID-19 patients, independent of changes in demographics or clinical factors at presentation, is likely due evolution of care, including clinical experience, decreasing hospital volume, use of new pharmacologic and nonpharmacologic treatments (proning) and earlier intervention
- Limitation: Single geographic region; potential for residual confounding by patient characteristics and admission thresholds
- See also: **Improving COVID-19 critical care mortality over time in England: A national cohort study, March to June 2020.** Dennis et al. medRxiv preprint. August 3**.**

Blood type

5. **Reduced prevalence of SARS-CoV-2 infection in ABO blood group O.** Barnkob et al. Blood Adv. October 14.
- A large study in Denmark compared risk of contracting SARS-CoV-2 and hospitalization/death from COVID-19 among ABO blood groups, including 473,654 individuals tested for SARS-CoV-2 and over 2.2 million non-tested individuals as the reference group
- Blood group O showed a RR of 0.87 (95% CI 0.83-0.91) for infection; while the RRs were 1.09 (1.04-1.14) for group A, 1.06 (0.99-1.14) for group B, and 1.15 (1.03, 1.27) for group AB
- No significant differences between blood groups for hospitalization or death from COVID-19.
- However, **see also: The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19.** Hoiland et al. Blood Adv. October 14.
- With a much smaller sample size, among 95 patients admitted to ICU in Vancouver hospitals, blood group A or AB showed a RR of 1.76 (1.17-2.65) for requiring ventilation and a RR of 3.75 (1.28-10.9) for requiring continuous renal replacement therapy vs. group O or B.
- Implications: Individuals with blood group A or AB may be at increased risk for contracting SARS-CoV-2 than those with blood group O. Whether there is a link between group A/AB and disease severity and the potential biological mechanisms require further research in larger patient cohorts

Convalescent plasma

6. **Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial).** Agarwal et al. BMJ. October 22**.**
- Open label, parallel arm, phase II, multicenter, randomized controlled trial conducted in 39 tertiary care public and private hospitals across India
- 464 adults admitted to hospital with confirmed moderate COVID-19 (partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200-300 mm Hg or a respiratory rate of more than 24/min with oxygen saturation (SpO_2) 93% or less on room air)
    - 235 assigned to convalescent plasma (2 doses of 200 mL 24 hours apart) with best standard of care (intervention) and 229 to best standard of care only (control)
- Virtually all donors were men, with a mean age of 34.3 (SD 9.3) years. Median disease duration was 6 days (IQR 3-11 days) and 94% of the donors had mild disease
- The primary outcome was a composite of progression to severe disease (PaO_2/FiO_2 ratio <100 mm Hg) any time within 28 days of enrolment or all-cause mortality at 28 days
- The composite outcome occurred in 44 (19%) patients in the intervention arm and 41 (18%) in the control arm (risk ratio 1.04, 95% confidence interval 0.71 to 1.54)

- Treatment with convalescent plasma was associated with a higher reporting of resolution of shortness of breath and fatigue among those survived to day 7
- A 20% higher rate of conversion to a negative result for SARS-CoV-2 RNA occurred on day 7 among patients in the intervention arm
- A statistically significant 20% higher rate of conversion to a negative result for SARS-CoV-2 RNA occurred on day 7 among patients in the intervention arm
- Limitations: Not blinded design; underpowered to examine timing of convalescent plasma administration in relation to symptom onset; could not measure the antibody titers in convalescent plasma before transfusion
- Implications: Despite observed antiviral action, there was limited clinical benefit of convalescent plasma as treatment for patients with moderate COVID-19, but a priori measurement of neutralizing antibody titers in donors and participants would be informative

Symptoms/clinical presentation

7. **Follow-up of adults with non-critical COVID-19 two months after symptoms' onset.** Carvalho-Schneider et al. Clin Microbiol Infection. October 5.

- Up to 60-day follow-up by phone of 150 non-critical (hospitalized or received outpatient care) adult COVID-19 patients in Tours, France
  - Excluded deceased, recipients of ICU care, resident of care facility, transfers to another healthcare facility, lost to follow-up at Day 30
- Persistent symptoms defined at Day 30 and Day 60 as weight loss ≥ 5%, grade 2-4 dyspnea, asthenia grade 3 or 4, persisting chest pain, palpitations, anosmia/ageusia, headache, cutaneous signs, arthralgia, myalgia, persisting digestive disorders, fever, sick leave
- Day 30: 68% ≥ 1 symptom; Day 60: 66% ≥ 1 symptom
  - Most frequent symptoms were (Day 30, Day 60) anosmia/ageusia (27.8%, 22.7%), flu-like symptoms (36.0%, 21.5%), chest pain (18.0%, 13.1%), digestive disorders (17.3%, 11.5%)
- Persisting symptoms associated with age 40-59, hospital admission, oxygen therapy, and abnormal auscultation at symptom onset
- Limitations: Small sample size; health professionals overrepresented (~50%); possible bias due to loss to follow-up
- Implications: Persistent symptoms are common up to 60 days post-diagnosis

8. **Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes.** Leisman et al. Lancet Respir Med. October 16**.**

- Rapid review of 25 COVID-19 studies, including 1245 patients; comparator groups included four trials each in sepsis (n=5320), cytokine release syndrome (n=72), and acute respiratory distress syndrome unrelated to COVID-19 (n=2767)
- Interleukin-6 (IL-6) concentrations in patients with COVID-19 showed moderate heterogeneity, with a range of 6.5–357.2 pg/mL
- Compared to the mean serum IL-6 concentration in patients with severe or critical COVID-19 (36.7 pg/m), mean concentrations were nearly 100 times higher in patients with cytokine release syndrome, 27 times higher in patients with sepsis, and 12 times higher in patients with non-COVID-19 acute respiratory distress syndrome (ARDS) ($p<0.0001$ for all comparisons)
- In contrast, several non-cytokine biomarkers, including D-dimer, C-reactive protein, and ferritin, are elevated to a similar or greater extent in patients with COVID-19 than in comparison patients
- Limitations: Single cross-sectional IL-6 measurement in many studies; possibility for treatment-induced (e.g., tocilizumab) IL-6 elevation cannot be ruled out

- Implications: Questions remain about the potential role of anti-cytokine treatments
- **See also: Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia.** Parr. JAMA Intern Med. October 20.

9. Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness. Pierron et al. Nature Comm. October 14.

- Participants living in France, Italy or the UK were extracted from the Global Consortium for Chemosensory Research survey (GCCR). Data were collected from April 7 to May 14 to study whether self-reported smell/taste changes are associated with hospital overload and are early markers of the spread of SARS-CoV-2 infection
- There was a strong relationship between self-reported chemosensory changes and the number of admissions to CCRUs (R_{smell}=0.88, p=8.9×10^{-8})
- The peak of onset of chemosensory changes appeared 4 days after lockdown. Conversely the governmental index of ratio of ER consults for suspicion of COVID-19 to general ER consultations only peaked 11 days after the lockdown, while the peak of CCRU administrations was shifted later by 14 days
- Implication: The incidence of sudden smell and taste change in the general population may be a cost-effective surveillance method for coronavirus spread and may represent an early marker of the effectiveness of governmental decisions
- Limitation: Correlation study; without large-scale validation studies and individual level data, causality cannot be assessed

HUMAN IMMUNE RESPONSE

10. Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low Prevalence Communities and Reveal Durable Humoral Immunity. Ripperger et al. Immunity. October 13.

- To improve the positive predictive value of serology/ELISA assays (especially in low prevalence areas), the use of an orthogonal antigenically distinct assay was assessed – receptor binding domain (RBD, in the S1 domain of Spike), nucleocapsid (N), and S2 domain of spike were considered as distinct antigens
    - confirmed COVID-19 samples showed very weak reactivity to N, suggesting it was not a good antigen for these assays
    - assessment of S2 serum reactivity suggested this is a better antigenically distinct protein for orthogonal assessment
    - inclusion of S2 as a requisite confirmatory screen markedly improved the positive predictive value of SARS-CoV-2 serological assays (empirically defined false positive rate of 0.02%)
- Individuals with severe disease (hospitalized) exhibited elevated virus-neutralizing titers and antibodies against N and the RBD of spike protein compared to symptomatic but not hospitalized; S2 titers were not statistically significantly different
    - All individuals seroconverted by 2 weeks post-PCR confirmation
- Spike RBD and S2 and neutralizing antibodies were detectible out to 5-7 months in some individuals, but antibodies to N were rarely above the threshold when assessed after 100 days
- Limitations: Immunity was defined as neutralization in a PRNT assay (which is a restrictive definition); unclear how using serological assay to measure anti-N was not good enough for the orthogonal assessment but good enough to measure anti-N decline over time
- Implications: Using orthogonally antigenically diverse antigens leads to highly specific serological assay for SARS-CoV-2 exposure that is usable in very low seroprevalence communities; the specific assays presented here return positive results that are highly consistent with virus neutralization

THERAPEUTIC/VACCINE DEVELOPMENT

11. **Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms.** Gordon et al. Science. October 15**.**

- This manuscript expanded on the published map of virus-host protein interactions for SARS-CoV-2 (PMID:32353859) mapping the interactomes of SARS-CoV-2 and MERS-CoV; investigated the localization of viral proteins identifying virus-human interactions
- Subcellular localization of proteins was assessed using expression in HeLaM then using immunofluorescence or using specific Ab raised against these viral proteins and infection of Caco2 cells; sometimes these agreed, but other times there was not agreement in localization between methods; most orthologous proteins have the same localization across the viruses
- Some proteins (M, N, Nsp7/8/13) showed a disproportionately high fraction of shared interactions conserved across the three viruses
- Up to 51% of protein interactions with a conserved human target occurred via a different (non-orthologous) viral protein
- SARS-specific interactions, MERS-CoV-specific interactions and interactions shared between all three CoV (casein kinase II and RNA processing regulators interacting with N protein; IMP dehydrogenase 2 (IMPDH2) interacting with Nsp14; centrosome, protein kinase A, and TBK1 interacting with Nsp13; and the signal recognition particle, 7SK snRNP, exosome, and ribosome biogenesis components interacting with Nsp8) were identified
- Genetic perturbations of 332 human proteins (including ACE2) in either A549 or Caco-2 cells were used to screen and identify host factors that SARS-CoV depends on for infectivity
    - 34 factors in A549 and 44 factors in Caco-2 cell experiments affected SARS-CoV-2 infectivity when perturbed
- Several dependent interactions are described including Nsp7 with prostaglandin E synthases (PGES2) 2, Orf8 with IL-17RA, Nsp6 with sigma receptor 1; Orf9 with mitochondrial import receptor subunit Tom70
- GWAS identified 14 SNPs near the IL17RA gene that could regulate sIL17RA plasma levels; these genotypes were associated with lower risk of COVID-19
- A small, non-interventional, retrospective study found that new users of indomethacin (which inhibits PGES2) in the outpatient setting were less likely than matched new users of celecoxib to require hospitalization or inpatient services for COVID-19
- Addressing the Nsp6-sigma1 interaction 13 FDA-approved drugs with reported nanomolar affinity for sigma receptors or that fit the sigma ligand chemotype were found to be potent inhibitors of SARS-CoV-2 with IC50 values under 10 µM.
- Comparing the effectiveness of typical antipsychotics, which have sigma activity and antiviral effects versus atypical antipsychotics (which do not), for treatment of COVID-19 in a retrospective analysis on new inpatient users, half as many new users of the sigma-ligand typical antipsychotics compared to users of atypical antipsychotics progressed to the point of requiring mechanical ventilation, demonstrating significantly lower use with an OR of 0.46 (95% CI = 0.23-0.93)
- Implications: Molecular insight can generate testable clinical hypotheses and help prioritize candidates for prospective clinical trials or future drug development

12. **SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies.** Barnes et al. Nature. October 12**.**

- Neutralization by candidate therapeutic human neutralizing antibodies (hNAbs) to SARS-CoV-2 occurs primarily by blocking the spike protein's receptor-binding domain interaction with ACE2 receptor

- Categorization of the structural correlates of neutralization that elucidate differences in mechanism and neutralization potency may aid therapeutic development of candidate hNAbs
- Both the structural features of an antibody that determine binding pose and the SARS-CoV-2 spike protein orientation in either the "up" or "down" position are critical in determining recognition
- Structural categories of ACE2 blocking hNAbs include:
    - those with *VH3-53* and short CDRH3s that only identify "up" RBDs
    - those that bind both "up" and "down" RBDs and can make contact with adjacent RBSs
    - those that bind outside the ACE2 binding site and recognize both "up" and "down" RBDs
- Structural insights provide information for rationally chosen antibody pairs which may limit the potential of viral escape of antibody pressures
- Amino acid differences in the RBD of various strains affect hNAb recognition and affinity.
- Limitation: Structural studies primarily rely on the use of single arm Fab proteins, whereas full length antibodies with two binding arms may have both unique mechanisms and implications in cocktail approaches
- Implications: Structural analysis of hNAb spike protein recognition provides a blueprint for both single and cocktail antibody therapeutics against SARS-CoV-2

13. **Unbiased screens show CD8+ T cells of COVID-19 patients recognize shared epitopes in SARS-CoV-2, most of which are not located in the Spike protein.** Ferretti et al. Immunity. October 20**.**

- Unbiased screens (termed T-Scan) identified SARS-CoV-2 targets of CD8+ T cells from 78 adult COVID-19 patients
    - CD8+ T cells were co-cultured with a genome-wide library of target cells (modified HEK 293 cells), engineered to express a single HLA allele; a target was identified when either the target underwent apoptosis and/or the T cells express granzyme B.
    - used NetMHC4.0 to identify specific, high-affinity peptides in each stretch of a.a.; synthesized peptides corresponding to each epitope to validate our findings; epitopes induced peptide-dependent T-cell activation as determined by interferon-gamma (IFNγ) secretion and CD137 upregulation
- CD8+ T cells predominantly recognize 3-8 shared epitopes for each HLA type studied; in total 29 CD8+ T cell epitopes were mapped and validated
    - ~90% of shared epitopes are not located in the Spike protein; epitopes are predominantly in the ORF1ab and the nucleocapsid protein
- CD8+ T cells show almost no cross-reactivity with epitopes in four commonly circulating coronaviruses, OC43, HKU1, NL63, and 229E
- Limitations: Study was underpowered to evaluate the clinical impact of CD8+ T cells recognizing specific epitopes; further evaluation needed to see if epitopes are associated with protection
- Implications: Epitopes identified could enable the design and evaluation of next-generation vaccines that more fully recapitulate the scope of natural CD8+ T cell responses to SARS-CoV-2 infection.

14. **Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates.** Walsh et al. NEJM. October 14**.**

- U.S. phase 1 trial data of two vaccine candidates in younger and older adults, interim safety and immunogenicity data is presented
- Healthy adults 18 to 55 years of age and those 65 to 85 years of age received either placebo or one of two lipid nanoparticle–formulated, nucleoside-modified RNA vaccine candidates (13 groups based on age and doses -(10 μg, 20 μg, 30 μg, and 100 μg):
    - BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor–binding domain

    - BNT162b2, which encodes a membrane-anchored SARS-CoV-2 full-length spike, stabilized in the prefusion conformation
- BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, particularly in older adults
    - i.e. 75% of the participants reported a temperature of 38.0°C or higher after the second 30-µg dose of BNT162b1; <17% reported after second dose BNT162b2
    - Fewer BNT162b2 recipients than BNT162b1 recipients reported using antipyretic or pain medication
- Antigen-binding IgG and virus-neutralizing responses to vaccination with 10 µg to 30 µg of BNT162b1 or BNT162b2 were boosted by the second dose in both the younger and older adults
    - Responses were similar or higher than the GMTs of a panel of SARS-CoV-2 convalescent serum samples (most moderate COVID 19 cases)
- Limitations: 100ug dose data was not presented (it was the outlier where only one dose was administered because of reactogenicity); no data available on cellular immune response to BNT162b2 yet; longevity of the response still needs assessed
- Implications: The BNT162b2 is ready to advance to a phase 2-3 trial

15. Decoy nanoparticles protect against COVID-19 by concurrently adsorbing viruses and inflammatory cytokines. Rao et al. PNAS. October 6**.**

- This manuscript reports on the development of an engineered cell membrane nanodecoy for COVID-19. The decoy design focused on both neutralization of virus and inflammatory cytokines.
- Human embryonic kidney cells (293T) were engineered to express the SARS-CoV2 receptor ACE2; cell membrane nanovesicles from these 293T/ACE2 cells were fused with cell membrane nanovesicles from human myeloid mononuclear THP1 cells (known to express several cytokine receptors).
    - Fusion was confirmed using fluorescent imaging of pre-labelled nanovesicles
    - TEM was used to confirm shape and size of the nanovesicles (100nm, round)
    - Western blotting confirmed that ACE2, CD130 (IL-6 receptor), and CD116 (GM-CSF receptor) were expressed on these nanovesicles
- Nanodecoys and 293T/ACE2-nanovesicles exhibited inhibitory activity against pseudotyped SARS-CoV-2, pseudotyped SARS-CoV and 2 SARSr-CoVs (SARs "related" CoV), and authentic SARS-CoV2 (in Vero-E6 and Caco-2 cells) significant at 1-5ug.
- Nanodecoys and THP-1 nanovesicles bound IL-6 and GM-CSF in solution; nanodecoys neutralized IL-6 and GM-CSF produced by THP-1 cells stimulated with LPS in a dose dependent manner (small impact seen at 1ug more significant at 20ug).
- In an in vivo acute lung inflammation model (mice challenges i.t. with LPS, 4 hr later received nanodecoy or control (PBS), 8 hr later BAL, 24 hr later histological assessment), nanodecoy at 200ug or 400ug reduced IL-6 and GM-CSF; some evidence of reduced lung injury in histological analysis with nanodecoys
- Limitations: Cellular infiltrates were not measured in mouse model to quantify changes; in vivo control was PBS rather than nanovesicles without pertinent receptors; only pilot systematic toxicity performed on mice
- Implications: Engineering decoy nanoparticles against COVID-19 could be an anti-viral and anti-inflammatory approach to therapeutics

Animal models

16. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Baum et al. Science. October 9**.**

- In vivo efficacy of 2 neutralizing antibody cocktail was assessed in both rhesus macaques (mild disease model) and golden hamsters (more severe)
- NHP receiving REGN-COV2 prophylaxis (50mg/kg i.v. and challenge with $1x10^5$ PFU in. and it 3 days post Ab dosing) had accelerated clearance of gRNA with almost no detectible sgRNA (replication); a lower dose of Ab (0.3mg/kg) was less efficient; NHP receiving REGN-COV2 treatment at day 1 p.i., there was accelerated clearance compared to placebo
    - interstitial pneumonia incidence (# of animals & # of lung lobes affected) and severity were reduced in both prophylactic and therapeutic treatment compared to placebo
- Hamsters receiving either 50, 5 or 0.5mg/kg of REGN-COV2 2 days before challenge with 2.3x10^4 PFU dose of SARS-CoV-2 virus were protected from weight loss, had decreased viral loads (but not significant), reduced alveolar infiltration and interstitial pneumonia compared to controls; a therapeutic benefit was observed in hamsters treated with 50mg/kg of REGN-COV2 1-day p.i. when assessing weight loss (trends but no significant differences in viral load or interstitial pneumonia
- Limitations: Study was small (groups of 4-5 animals) and could be underpowered; need to assess the effectiveness of this treatment on the D614G variant of SARS-CoV2; questionable feasibility of treating at one day post infection
- Implications: Therapeutic potential with these antibodies if administered early (late has not been investigated)

17. **Vascular Disease and Thrombosis in SARS-CoV-2- Infected Rhesus Macaques.** Aid et al. Cell (in press). November 25**.**

- Endothelial disruption and vascular thrombosis were observed in histopathologic sections of lungs from both humans (autopsies) and rhesus macaques infected with SARS-CoV-2 (Day 2 and 4)
- Transcriptomic analyses of BAL and peripheral blood from macaques & proteomic analyses of serum was performed (Day 1-14)
    - significant enrichment of gene/protein signatures associated with coagulation, thrombosis, and vascular disease
    - pathways of coagulation and clotting cascade were increased
    - markers of platelet activation and aggregation and extracellular matrix organization
    - increased expression of many components of the complement pathway
    - Ingenuity pathway analysis showed increases in IFN response genes (both g & a), TNF signaling; responses waned by day 10-14 post infection in macaques (several were confirmed with Immunohistochemistry in the lung tissue)
- Increases in cytokines and chemokines involved in recruitment of macs, PMNs, B cells
- Large numbers of macrophages (CD68+ and CD163+) and CD16+ cells were found in the airways and alveoli of the infected macaques using cyclic immunofluorescence; inflammatory (M1) gene profiles were more upregulated than M0 or M2 (anti-inflammatory) profiles
- Limitations: Time course of disease in macaques (peaks at day 2, yet resolves quickly)
- Implications: The macaque model may be useful for evaluating potential therapeutics which target these interactions between inflammatory and thrombosis pathways