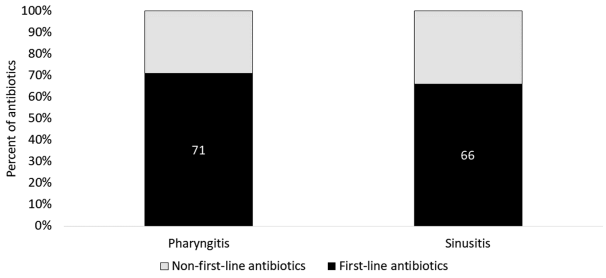

Figure 2. Percent of first-line antibiotics versus non-first-line antibiotics prescribed for pharyngitis and sinusitis. First-line antibiotics were defined as penicillins (e.g., penicillin, amoxicillin) for pharyngitis and penicillins or beta-lactams with increased activity (e.g. amoxicillin/clavulanate) for sinusitis.

Disclosures. **All Authors:** No reported Disclosures.

970. Antibiotic Use Variability Among US Nursing Homes—2016

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Session: 124. Out of the Box and Out of the Hospital: Stewardship Outpatient Services
Friday, October 4, 2019: 11:30 AM

Background. Antibiotics are frequently prescribed in nursing homes (NH). National data describing facility-level antibiotic use (AU) in NH are lacking. The objectives of this analysis were to use NH electronic health records (EHR) to describe AU in NH and variability in AU rates across NH.

Methods. We analyzed antibiotic orders for 309,884 residents in 1,664 US NHs using one EHR company in 2016. We calculated AU rates as antibiotic days-of-therapy (DOT) per 1,000 resident-days and compared by the type of stay (short-stay (SS) ≤ 100 days vs. long-stay (LS) >100 days). We also examined prescribing indications and the duration of nursing home-initiated antibiotic orders. We assessed facility-level correlates of AU using resident health and NH facility characteristics publically available through NH Compare and LTCfocus using a univariate linear regression.

Results. In 2016, 57% of NH residents received at least one systemic antibiotic; overall rate of AU was 90 DOT/1,000 resident-days. The median facility-level AU rate was 64 DOT/1,000 resident-days (IQR 36–104). The median proportion of SS residents at a facility was 74% (IQR 60–84%). The SS and LS AU rates were 241 DOT/1,000 resident-days (IQR 173–342) and 24 DOT/1,000 resident-days (IQR 14–37), respectively. Overall, the three most common antibiotic classes prescribed were fluoroquinolones (18%), cephalosporins (18%), and extended-spectrum β-lactams (10%). Antibiotics were most frequently prescribed for urinary tract infections, and the mean duration of an antibiotic order was 9 days (range 1–365). Higher facility AU rate correlated positively with the following facility characteristics; proportion of SS residents, urban location, proportion of residents with mild cognitive impairment and lower activities of daily living scores, presence of ventilator beds, proportion of LS residents with urinary catheters or pressure ulcers, facility case-mix index, and not-for-profit ownership and multiorganization facilities.

Conclusion. Significant variability in NH AU rates exist, and SS residents have higher AU rates. Identifying NH with high rates of AU after adjusting for facility-level predictors of AU may identify opportunities for targeting efforts to improve prescribing practices.

Disclosures. **All Authors:** No reported Disclosures.

971. The Role of Inflammation and Innate Effectors in Passive Immunization for Acinetobacter baumannii Infections

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Session: 125. Pathogenesis and Inflammatory Response
Friday, October 4, 2019: 10:30 AM

Background. We have previously demonstrated that *A. baumannii* virulence is driven by avoidance of innate effector clearance, resulting in LPS-TLR4 triggering of excess inflammation in the host. We also raised a monoclonal antibody (MAb) that improved survival of mice lethally infected with *A. baumannii*.

Methods. Mice were selectively depleted of innate effectors (macrophages with liposomal clodronate, neutrophils with cyclophosphamide, and/or complement with cobra venom factor), infected with an XDR clinical blood isolate of *A. baumannii*, and treated with placebo or anti-*A. baumannii* MAb.

Results. Single disruption of macrophages or neutrophils did not enhance lethality but complement deficiency did. In contrast, singly disrupting complement or neutrophils did not impact bacterial density but macrophage disruption markedly increased it. Thus, a dissociation of bacterial density and survival was observed. MAb therapy was completely protective in mice depleted of a single effector. While dual depletion resulted in diminished MAb efficacy in terms of survival, mice retaining neutrophils had marked improvements in survival with MAb therapy compared with other dual-depletion groups. The dissociation of bacterial density and survival suggested that inflammation was a primary driver of host outcome. Levels of IL-10 and TNFα had a reciprocal relationship in mice across effector depletion groups and were lower in mouse groups with higher survival when adjusted for bacterial density. IL-10 disruption completely abrogated the survival benefit of MAb therapy without altering bacterial clearance mediated by MAb. In contrast, TNFα disruption enhanced MAb efficacy for survival, and the presence of TNFα was antagonistic to MAb efficacy.

Conclusion. These results confirm that host outcomes from *A. baumannii* infection are driven by host inflammatory response rather than bacterial density alone. Furthermore, novel therapeutic approaches seeking to improve outcomes from such infections must seek to shift the balance of pro-/anti-inflammatory cytokines to favor a down-modulated inflammatory response.

Disclosures. **All Authors:** No reported Disclosures.

972. A Mycobacterium tuberculosis Secreted Lipid Triggers Cough Through a Neuronal Cough Receptor

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Session: 125. Pathogenesis and Inflammatory Response
Friday, October 4, 2019: 10:45 AM

Background. A hallmark symptom of active pulmonary tuberculosis vital for disease transmission is cough. The current paradigm for tuberculosis-related cough is that it results from airway damage or irritation. However, there is limited experimental data to support this theory, and whether *Mycobacterium tuberculosis* (Mtb) induces cough to facilitate its own transmission has not been explored. The cough reflex is a complex and coordinated event involving both the nervous and musculoskeletal systems initiated by particulate or chemical molecules activating nociceptive neurons, which sense pain or irritation. This activation induces a signaling cascade ultimately resulting in a cough. Respiratory nociceptive neurons innervate the airway of humans and most mammals and thus are poised to respond to noxious molecules to help protect the lung from damage. Because Mtb is a lung pathogen, cough is a primary mechanism of Mtb transmission, and respiratory nociceptive neurons activate cough, we hypothesized that Mtb produces molecules that stimulate cough thereby facilitating its spread from infected to uninfected individuals. We previously identified a cough molecule produced by Mtb, and in this work characterize its neuronal receptor using genetics, biochemistry, and pharmacology.

Methods. We used an *in vitro* neuronal activation bioassay to study Mtb cough-inducing molecules. We also used a biochemical assay to identify the cough receptor. Finally, we used gene silencing, biochemistry, and pharmacologic inhibition to validate and characterize the activity of the newly discovered cough receptor.

Results. We isolated a complex lipid produced by Mtb that activates nociceptive neurons. Both an organic Mtb extract and the purified molecule alone were sufficient to induce cough in a conscious guinea pig cough model and guinea pigs infected with wild-type Mtb cough much more frequently than guinea pigs infected with Mtb strains unable to produce nociceptive molecules. Using genetics, biochemistry, and pharmacology techniques, we identified and validated a cough receptor for the Mtb lipid expressed on nociceptive neurons.

Conclusion. We conclude that Mtb produces a molecule that activates nociceptive neurons and induces cough through a specific neuronal receptor. These findings have significant implications for our understanding of Mtb transmission.

Disclosures. **All Authors:** No reported Disclosures.

973. Single-cell RNA Sequencing Analysis of Zika Virus Infection in Human Stem Cell-Derived Cerebral Organoids

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Session: 125. Pathogenesis and Inflammatory Response
Friday, October 4, 2019: 11:00 AM

Background. The molecular mechanisms underpinning the neurologic and congenital pathologies caused by Zika virus (ZIKV) infection remain poorly understood. One barrier has been the lack of relevant model systems for the developing human brain; however, thanks to advances in the stem cell field, we can now evaluate ZIKV central nervous system infections in human stem cell-derived cerebral organoids which recapitulate complex 3-dimensional neural architecture.

Methods. We apply Seq-Well—a simple, portable platform for massively parallel single-cell RNA sequencing—to characterize cerebral organoids infected with ZIKV. Using this sequencing method, and published transcriptional profiles, we identify

multiple cellular populations in our organoids, including neuroprogenitor cells, intermediate progenitor cells, and terminally differentiated neurons. We detect and quantify host mRNA transcripts and viral RNA with single-cell resolution, defining transcriptional features of uninfected cells and infected cells.

Results. In this model of the developing brain, we identify preferred tropisms of ZIKV infection and pronounced effects on cell division, differentiation, and death. Our data additionally reveal differences in cellular populations and gene expression within organoids infected by historic and contemporary ZIKV strains from a variety of geographic locations. This finding might help explain phenotypic differences attributed to the viruses, including variable propensity to cause microcephaly.

Conclusion. Overall, our work provides insight into normal and diseased human brain development, and suggests that both virus replication and host response mechanisms underlie the neuropathology of ZIKV infection.

Disclosures. **All Authors:** No reported Disclosures.

974. PD-1 Immune Checkpoint Blockade Improves Survival and Promotes Fungal Clearance in an Immunosuppressed Murine Invasive Pulmonary Aspergillosis (IPA) Model

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Session: 125. Pathogenesis and Inflammatory Response

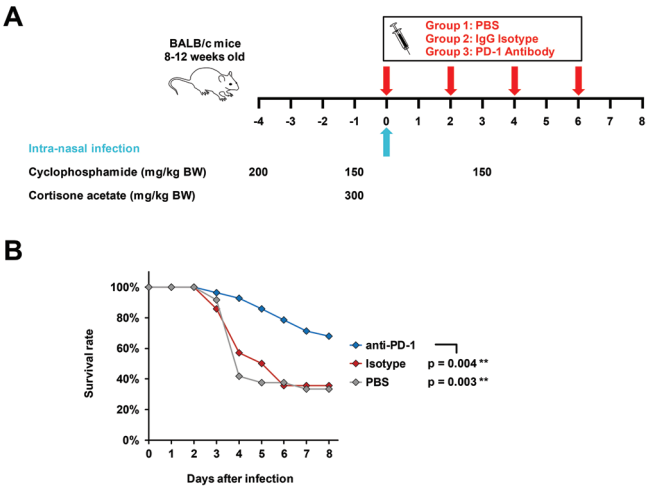
Friday, October 4, 2019: 11:15 AM

Background. Checkpoint blockade (CPB) has brought a revolution in modern oncology and may offer new strategies for antifungal immunotherapy. *In vitro* studies have demonstrated that blockade of the PD-1/PDL-1 interaction increased IFN-γ secretion in response to *Aspergillus* antigens, suggesting a potential role for anti-PD-1 therapy in promoting anti-*Aspergillus* immunity. We sought to evaluate the therapeutic efficacy of low-dose anti-PD-1 therapy in a murine IPA model.

Methods. Eight- to twelve-week-old female BALB/c mice were immunosuppressed with cyclophosphamide and cortisone acetate and infected intra-nasally with 5×10^4 of *A. fumigatus* Af293 conidia (panel A). Mice were then treated intraperitoneally with 4 doses of either 200 µL PBS (PBS control), 250 µg/kg BW IgG antibody (isotype control), or a monoclonal PD-1 antibody (anti-PD-1). Survival was monitored daily until day 8 post-infection. 24–28 mice per treatment were assessed in 3 independent experiments. Pulmonary fungal burden was determined by 18S qPCR either on day 8 post-infection or upon death. Additional mice were sacrificed on day 1 and 4 post-infection to assess serum concentrations of selected cytokines by ELISA.

Results. Infected mice receiving treatment with either PBS or the isotype antibody exhibited 8 day survival rates of 33% and 36%, respectively. In contrast, 68% of the mice in the PD-1 antibody treatment group survived (panel B). Accordingly, pulmonary fungal burden was significantly reduced in anti-PD-1 vs. isotype-treated infected mice (median spore equivalent: 0.39 vs. 2.06×10^9, $P = 0.015$). No signs of toxicity or early mortality were seen in anti-PD-1-treated mice, and no elevated serum levels of pro-inflammatory cytokines TNF-α and INF-γ were found in those mice (compared with isotype-treated infected mice).

Conclusion. We found that anti-PD-1 immune checkpoint blockade has independent beneficial effects in untreated immunosuppressed mice with IPA. We are in the process of measuring pulmonary cytokines to deepen our understanding of protective anti-*Aspergillus* immunity conferred by low-dose CPB. In addition, future studies would address the combined application of CPB and conventional antifungal drugs that have immune-regulatory activity such as echinocandins.



Disclosures. **All Authors:** No reported Disclosures.

975. Roles of Type I and III Interferon in Severe Pathogenesis of Human Metapneumovirus

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Session: 125. Pathogenesis and Inflammatory Response

Friday, October 4, 2019: 11:30 AM

Background. Human metapneumovirus (HMPV) is a leading cause of respiratory tract infection in children and adults. However, mechanisms of pathogenesis are not fully understood.

Methods. We tested HMPV clinical and laboratory isolates in an established C57BL/6 mouse model and measured weight loss, airway function, and viral titers. Immune responses were determined using cytokine quantitation and flow cytometry.

Results. HMPV clinical isolates induced variable disease severity ranging from mild to fatal disease. Laboratory strain TN/94-49 did not cause weight loss, but mice infected with clinical isolate C2-202 showed dramatic weight loss and 40% mortality within 5 days post-infection (Figure 1). These findings were confirmed in other inbred mouse strains. C2-202-infected mice also suffered from impaired pulmonary function post-recovery. Lung viral titer did not correlate with disease severity, suggesting immune-mediated pathogenesis. C2-202-infected mice exhibited increased production of type I and III interferons (IFN) and pro-inflammatory cytokines, and lung neutrophil infiltration. However, neutrophil depletion or inflammasome inactivation did not reduce disease. Stat1/Stat2 double knockout (KO) mice lacking type I and III IFN signaling exhibited reduced weight loss but increased lung viral titer after C2-202 infection (Figure 2). Type I IFN receptor (IFNAR) KO mice infected with C2-202 had reduced weight loss but unchanged lung viral titer (Figure 3), while the addition of type III IFN blockade to C2-202-infected IFNAR mice had no effect on disease but increased lung viral titer (Figure 4).

Conclusion. These results suggest that severe disease caused by virulent HMPV was due to exuberant IFN response. Moreover, type I IFN was primarily associated with disease, while type III IFN was associated with viral clearance. These data suggest that IFN signaling plays an important role in HMPV pathogenesis, and thus serves as a potential therapeutic target.

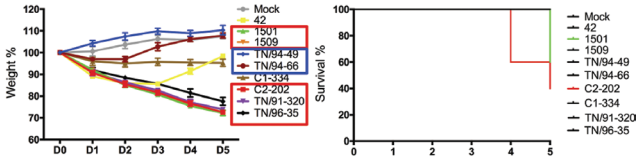

Fig. 1. HMPV clinical isolates are more virulent than laboratory strains. Weight loss curves (left) and mortality (right) of mice infected with HMPV lab strains (blue box) and clinical isolates (red boxes).

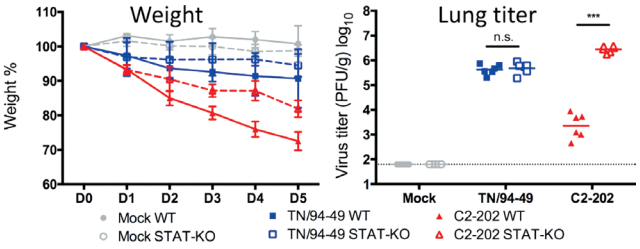

Fig. 2. Type I and III IFN signaling through STAT1/STAT2 mediate disease and contorl viral replication. Weight loss curves (left) and lung virus (right) of STAT1/STAT2 double KOmice infected with HMPV lab strain TN/94-49 (blue) and clinical isolate C2-202 (red).

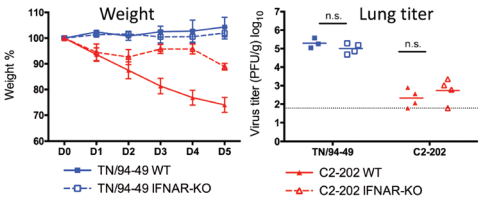

Fig.3. Type I IFN contributes to disease but fails to limit viral replication. Weight loss curves (left) and lung virus titer (right) of IFNAR knockout mice infected with HMPV lab strain TN/94-49 (blue) and clinical isolate C2-202 (red).

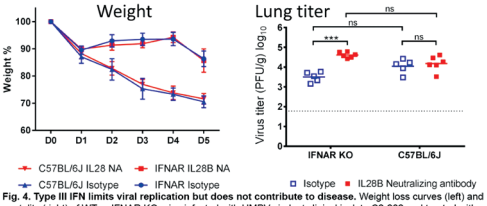

Fig. 4. Type III IFN limits viral replication but does not contribute to disease. Weight loss curves (left) and mortality (right) of WT or IFNAR KO mice infected with HMPV virulent clinical isolate C2-202 and treated with IL-28B neutralizing antibody (red) or isotype control antibody (blue).

Disclosures. **All Authors:** No reported Disclosures.