multiple cellular populations in our organoids, including neuroprogenitor cells, inter-
mediate progenitor cells, and terminally differentiated neurons. We detect and quantify
host mRNA transcripts and viral RNA with single-cell resolution, defining transcription-
al 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 mecha-
nisms 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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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 × 106 of A. fumigatus AF293 conidia (panel A). Mice were then treated intra-
peritoneally 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 anti-
body 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 × 107, 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 inde-
pendent 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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Background. Human metapneumovirus (HMPV) is a leading cause of respira-
tory 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. However, 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.

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