SARS-CoV-2 Research Summary
Omicron (BA.1) Replication and Pathogenesis

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Introduction

The rapid rise of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Omicron variant of concern (VOC), has led to a large number of studies detailing this variant's ability to replicate both *in vitro* and *in vivo* models. These studies provide evidence for significant changes in the viral life cycle, including changes to viral entry, transmission and pathogenicity. Below we have compiled a list of such studies and have attempted to provide a brief summary of the main themes each presents.

Major Conclusions

- Omicron replication was reduced in multiple TMPRSS2-expressing cell lines, but was able to efficiently infect through endosomal fusion.
- *In silico* and *in vitro* studies show omicron may have a more stable Spike (S) protein.
- Omicron S showed less efficient cleavage and reduced cell:cell fusion, compared to previous variants.
- Omicron may have reduced ability to antagonize host cell interferon response
- Omicron had reduced pathogenicity *in vivo* in mice and hamster animal models, and resulted in less severe disease.
- Omicron had lower viral loads in respiratory tracts of animal models, but higher in nasal turbinates.

Title	Brief Summary
HKUMed finds Omicron SARS-CoV-2 can infect faster and better than Delta in human bronchus but with less severe infection in lung	This study used live virus (LV) and ex-vivo (human) respiratory tract cultures to compare viral replication of wild type (WT), Delta and Omicron variants. Results indicated that Omicron replicated faster and at higher levels than WT and Delta in bronchus tissues. However Omicron was less efficient than WT and Delta at replication in lung tissues.
SARS-CoV-2 Omicron spike mediated immune escape, infectivity and cell-cell fusion	This study used pseudotyped virus (PV) to compare viral replication of Omicron and Delta variants in lower airway organoids and Calu-3 lung cells. Results indicated that: 1) Omicron spike had reduced cleavage efficiency compared to Delta, 2) Omicron PV had inefficient entry into lower airway organoids and Calu-3 lung cells, 3) Omicron was less efficient ar entry into TMPRSS2 expressing cells than Delta, and 4) Reduced cell-cell fusion compared to Delta
Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant	This study used LV to assess infectivity & pathogenesis in hamsters. Results indicated that: 1) Omicron was less fusogenic than WT and Delta, 2) Omicron S protein is less efficiently cleaved than Delta, and 3) Omicron was poorly infectious,had efficient transmission and was less pathogenic in hamsters.
The SARS-CoV-2 B.1.1.529 Omicron virus causes attenuated infection and disease in mice and hamsters	This study used Omicron LV to assess infectivity and pathogenesis in ACE2 (hACE2) expressing mice and hamsters. Infection was attenuated in 129, C57BL/6, and BALB/c mice compared with other SARS-CoV-2 variants

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The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism	This study used LV and PV to assess viral entry and fusion. Results indicated that Omicron favored a TMPRSS2-independent endosomal fusion mechanism rather than cell surface fusion. Cell-cell fusion or syncytia was not observed with Omicron, as with previous variants. Omicron viral replication was aso attenuated in Calu-3 human lung epithelial cells.
SARS-CoV-2 Omicron-B.1.1.529 Variant leads to less severe disease than Pango B and Delta variants strains in a mouse model of severe COVID-19	This study used LV in a K18-hACE2 mouse model to assess Omicron disease severity compared to Pango B and Delta variants. Compared to other variants, Omicron infected mice had: 1) less severe clinical signs (weight loss), 2) faster recovery, 3) lower virus load in lower and upper respiratory tract, and 4) less extensive inflammatory processes in the lungs.
The omicron (B.1.1.529) SARS-CoV-2 variant of concern does not readily infect Syrian hamsters	This study used LV to compare infectivity and pathogenesis of Omicron versus an ancestral D614G strain in hamsters. Results for Omicron indicated, 1) lower viral loads in the lungs, 2) no infectious virus detectable in lungs, and 3) no signs of peri-bronchial inflammation or bronchopneumonia.
Reduced Pathogenicity of the SARS-CoV-2 Omicron Variant in Hamsters	This study used LV to compare infectivity and pathogenesis of WA1/2020, Alpha, Beta, Delta, and Omicron strains strain in hamsters. Results for Omicron indicated, 1) no detectable weight loss, 2) lower viral loads in lung parenchyma, but a trend towards higher viral loads in nasal turbinates.
Neutralization and Stability of SARS-CoV-2 Omicron Variant	This study PV to assess viral entry, replication and fusion in HEK293T-ACE2 cell line. Omicron showed reduced receptor binding, cell-cell fusion, and S1 subunit shedding. However, Omicron had increased cell-to-cell transmission, and homology modeling predicted a more stable closed S structure.
Reduced interferon antagonism but similar drug sensitivity in Omicron variant compared to Delta variant SARS-CoV-2 isolates	This study used LV to compare Delta and Omicron replication *in vitro* (Calu-3, Caco-2, Vero cells) and *in vivo* (hamsters). Authors stated that Omicron displayed a reduced infection capacity, except in interferon-deficient Vero cells, suggesting reduced ability to antagonize host cell interferon response.
The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry	This study used LV and PV to assess viral entry and fusion. Results indicated that, 1) Omicron replicated more rapidly than Delta in human primary airway cultures, 2) reduced syncytia formation, and 3) was capable of efficient endosomal viral entry in a TMPRSS2-independent manner.
Convalescence from prototype SARS-CoV-2 protects Syrian hamsters from disease caused by the Omicron variant	This study used LV *in vitro* (Vero cells) and *in vivo* (hamsters) to assess viral entry and fusion. Results indicated that Omicron, 1) caused less severe disease in hamsters compared to an ancestral strain, 2) hamsters re-challenged with Omicron after 50 days resulted in no clinical disease and rapid viral clearance.
Infectious viral load in unvaccinated and vaccinated patients infected with SARS-CoV-2 WT, Delta and Omicron	This study examined viral load in patients infected with SARS-CoV-2 WT, Delta and Omicron. Results included, 1) no correlation between RNA copy number and infectious virus titre (IVT), 2) Omicron vaccine breakthrough infections did not show elevated IVTs compared to Delta, 3) vaccinated individuals had lower IVT and cleared virus faster than unvaccinated individuals.

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Title	Brief Summary
The SARS-CoV-2 Omicron (B.1.1.529) variant exhibits altered pathogenicity, transmissibility, and fitness in the golden Syrian hamster model	This study used LV to compare Omicron and Delta *in vivo* pathogenicity, transmissibility, and fitness. Omicron showed less pathogenecity in hamster compared to Delta: less body weight losses, clinical scores, respiratory tract viral burdens, cytokine/chemokine dysregulation, and tissue damage. Transmission studies showed that Omicron had 10-20% higher transmissibility than Delta. Omicron was also able to outcompete Delta under immune selection pressure
SARS-CoV-2 Omicron efficiently infects human airway, but not alveolar epithelium	This study used human airway and alveolar organoids to explore shedding, fitness, and virulence of Omicron pseudo virus. Omicron replicated efficiently in the human airway, but not in the alveoli; did not efficiently use TMPRSS2 for entry.