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# Persistent Immune Imbalance in Post-Acute Sequelae of SARS-CoV-2: Neutrophil-Driven Pathology and Therapeutic Strategies from a P. roborovskii Hamster Model

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Post-acute sequelae of SARS-CoV-2 (PASC), affects at least 10% of COVID-19 patients, yet its mechanisms remain unclear. Using Phodopus roborovskii hamsters as animal models, we compared outcomes following infection with SARS-CoV-2 and H1N1 influenza A virus (IAV). Among SARS-CoV-2-infected survivors, 13.75% exhibited delayed recovery, severe pulmonary injury, and persistent weight loss, and were classified as the PASC group. Single-cell transcriptomic profiling of bronchoalveolar lavage fluid, lung, and spleen at 30 days post-infection (dpi) revealed PASC-specific gene signatures, with prominent neutrophil infiltration and reduced macrophage populations, indicating skewed myeloid differentiation. Immunohistochemical analysis confirmed persistent SARS-CoV-2 spike S1 antigen in the lungs of PASC hamsters at 30 dpi, co-localizing with dense neutrophilic infiltrates. Neutrophils from the PASC group showed prolonged expression of inflammatory genes (FPR2, MMP9, and S100A9) linked to neutrophil degranulation and extracellular trap formation. Targeted inhibition of neutrophil-associated pathways, particularly with the

neutrophil elastase inhibitor Sivelestat, effectively reduced neutrophilic inflammation, PASC incidence, and mortality. Our findings implicate persistent neutrophil activation as a key driver of PASC pathogenesis and suggest neutrophil-targeted therapies as promising strategies to alleviate chronic complications following SARS-CoV-2 infection.