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Role of angiotensin II in SARS-CoV-2 pathophysiology in a hamster model of COVID-19

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OBJECTIVES/GOALS: Hamsters develop COVID-19 similarly to people because the SARS-CoV-2 spike protein binds with high affinity to hamster ACE2 resulting in host cell entry and replication. Our goal was to establish a hamster model that mirrors the lung and brain pathophysiology observed in COVID-19. METHODS/STUDY POPULATION: Hamsters infected with SARS CoV-2 are sacrificed on day 1 and day 6 postinfection. Lung histopathology scoring model was implemented for assessment all pathological relevant changes in the lungs of infected animals on tissue sections stained with hematoxylin and eosin. To quantify the extent and severity of lung pathology, two scoring systems were used: the first evaluated all relevant changes in the lungs of the infected animals and the second evaluated only the pathology associated with the pulmonary vasculature. Percentage of airway affected, airway severity, bronchiolar epithelial hyperplasia, alveoli affected, alveolar severity, type II pneumocyte hyperplasia and vessels affected were analyzed. Total airway score plus total lung alveolar score give lung histopathology score. RESULTS/ANTICIPATED RESULTS: Compared to the control hamster, the hamsters day 1 postinfection, exhibited a higher total airway score [9.00 ± 1.35 vs. 0.25 ± 0.1; p DISCUSSION/SIGNIFICANCE: Establishing this outstanding small animal model of COVID-19 will facilitate studies investigating diagnostics, prognosis and response to treatment in COVID-19 disease. These studies will provide insights that will complement on-going clinical trials on angiotensin type 1 receptor (AT1R) blockers (ARBs) in COVID-19.

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Southeastern Wisconsin Community-Based Participatory Research using the All of Us Researcher Workbench

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OBJECTIVES/GOALS: Using a community-based participatory research (CBPR) approach, the All of Us (AoU) Wisconsin Froedtert & the Medical College of Wisconsin (MCW) site aimed to improve public understanding of science by creating a Special Interest Group (SIG) of community members and scientists and driving healthcare research relevant to Southeastern Wisconsin. METHODS/STUDY POPULATION: We recruited community members from the AoU advisory boards and scientists from Froedtert & MCW. These SIG participants will converge on a hypothesis that aligns with community priorities and conduct research using the national AoU database, which combines EHR, survey, and whole genome sequencing data. A year of monthly SIG meetings from 2022-2023 will serve as focus group sessions that will be recorded and transcribed. In addition to descriptive statistics on participant demographics and affiliations, we plan to qualitatively characterize transcripts, field notes, and feedback, such as participation satisfaction or reflection on self- and group-driven impact. We will publish alongside all SIG members on both the research outcomes and the SIG-driven process to inform future similar endeavors. RESULTS/ANTICIPATED RESULTS: To date, we held three SIG meetings, which together formed the discover and define stages in the human-centered design framework. We narrowed down SIG membership to 15 consistent participants. Our coalition building conversations emphasized group priorities and future payoffs for independent research and community partnerships. Realizing a crucial need for bioinformaticians to prosecute SIG-driven research questions, we created a data subgroup of trainees and scientists to familiarize themselves with the AoU Researcher Workbench. Through shared decision making during this community engaged process, we are converging on a research direction centering on specific diseases or adverse outcomes with relevance to Southeastern Wisconsin communities and with implications for personalized medicine. DISCUSSION/SIGNIFICANCE: SIG scientists will learn about CBPR and access the AoU database. SIG community members will better understand the research process and share their lessons with local communities. The AoU Wisconsin research team will disseminate findings on the collective research process and empower scientist use of this nationally curated AoU database.

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Team Science

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OBJECTIVES/GOALS: T develop a novel PROTAC to deplete BRK to inhibit tumorigenesis and metastasis, which is unattainable by using tradition kinase inhibitors. METHODS/STUDY POPULATION: We will design, synthesize, and evaluate BRK-specific PROTACs to study both catalytic and scaffolding properties of BRK that contribute to cancer progression. Optimal PRTOAC concentrations will be used to treat MDA-MB-231 cells to determine effects on cell proliferation, cell migration, invasion, metastatic potential, and colony formation. Immunoblotting will be used to determine target protein degradation and to evaluate if PROTAC mediated degradation of BRK allows SMAD4 to form complex with SMAD2 and SMAD3. Finally, a metastatic xenograft mouse model (MDA-MD-231) will be injected subcutaneously or via tail vein into NU/J 002019 mice8, 17 and treated with the BRK PROTAC to evaluate inhibition of tumorigenesis and metastasis. RESULTS/ANTICIPATED RESULTS: We expect that the PROTAC will specifically degrade BRK and restore the anti-tumorigenic and anti-metastatic function of SMAD4 in metastatic breast cancer. In turn, we anticipate that cell proliferation, invasion, and colony formation properties of metastatic breast cancer will be restricted and SMAD4 will form complex with SMAD2 and SMAD3. Additionally, mice treated the BRK targeted PROTAC should experience reduced tumor growth and metastasis compared to placebo. DISCUSSION/SIGNIFICANCE: This substantially new approach will inhibit oncogenic nRTKs to restore the antitumor function of TGFβ/SMAD signaling is expected to bring metastatic cancer under therapeutic control. Thus, the expected outcomes are likely to have a significant impact because it will provide a new targeted therapy to improve metastatic TNBC patient survival.

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