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From hypertension to fibroids: Translating cardiovascular therapeutics for women's health

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OBJECTIVES/GOALS: To investigate renin–angiotensin system (RAS) modulation as a therapeutic target for uterine fibroids using a xenograft model, translating insights from cardiometabolic–fibroid comorbidity into accessible treatment strategies for underserved populations. METHODS/STUDY POPULATION: We established a xenograft model by implanting matched human fibroid and myometrial tissue into NOG mice (n=6 per group) supplemented with estrogen pellets. This translational model mimics the clinical context of hypertensive patients with fibroids treated with RAS-modulating drugs. Mice were randomized to receive angiotensin II, losartan, enalapril, or vehicle control. Tumor volumes were measured weekly by caliper. At endpoint, xenografts are analyzed for proliferation (Ki67), fibrosis (α-SMA, collagen), and immune composition using flow cytometry and immunofluorescence. RESULTS/ANTICIPATED RESULTS: Preliminary data from all 24 mice reveal variable fibroid xenograft growth across treatment groups, with no consistent dose–response pattern in gross tumor volumes. Ongoing molecular and cellular analyses may uncover treatment effects not reflected in volume measurements alone. Final analyses will integrate proliferative indices, fibrotic markers, and immune cell profiles to determine whether RAS modulation influences fibroid biology at the cellular level despite heterogeneous morphological responses. DISCUSSION/SIGNIFICANCE OF IMPACT: Fibroids disproportionately affect Black women and are closely linked to cardiovascular disease. Repurposing FDA-approved antihypertensives offers an accessible, low-cost therapeutic avenue and exemplifies translational science by bridging mechanistic discovery with equitable treatment innovation.

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KEAP1–Nrf2 licenses natural killer cell effector fitness

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OBJECTIVES/GOALS: This work seeks to elucidate the upstream and downstream circuitry of the Keap1–Nrf2 axis in natural killer (NK) cells. We aim to define how the Keap1–Nrf2 axis sets a redox license to calibrate NK function and metabolic fitness, and in turn, to translate these findings into new strategies for metabolically enhancing NK and CAR-NK-based immunotherapy. METHODS/STUDY POPULATION: Keap1 and Nrf2 were investigated primarily in murine models, by using NK-specific knockouts of each gene (Ncr1Cre-Nrf2fl/fl and Ncr1Cre-Keap1fl/fl) in C57BL/6 mice. Flow cytometry was used to profile knockout versus wild-type differences in lymphocyte populations and subpopulations, including receptor repertoire, maturation, and effector function. *In vitro* and *ex vivo* experiments were performed by sorting cells from the spleens of knockout mice and their wild-type littermates. Human NK cells from healthy donors were analyzed with collaborators to validate the importance of the axis for human patients. RESULTS/ANTICIPATED RESULTS: Transcriptomics analysis of NK cells during murine cytomegalovirus (MCMV) infection revealed reciprocal regulation of Nrf2 and Keap1, with Nrf2 transcripts downregulated and Keap1 upregulated at day 4 post-infection, highlighting the potential contribution of this pathway to NK cell responses during viral challenge. We demonstrate that both insufficient and excessive ROS buffering impair host survival in response to MCMV and acute myeloid leukemia (AML) and compromise control of tumor metastasis in melanoma models. Importantly, both knockout models also exhibited defects in NK cell expansion, maturation, and cytotoxicity. Ongoing studies map the metabolic, epigenetic and transcriptional programs downstream of this pathway in both murine and human NK cells. DISCUSSION/SIGNIFICANCE OF IMPACT: As immunotherapies are developed and optimized, a rigorous understanding of the mechanisms through which immune cells kill pathogens is critical. Collectively, our work thus far identifies the Keap1–Nrf2 axis as a critical regulator of NK cell fitness that can be used to promote cell therapeutic development.

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Data COUNTS in Nebraska and beyond: Connecting CTSA and IDeA-CTR networks for scalable translational science

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OBJECTIVES/GOALS: The NIH Office of Data Science and Strategy created Data COUNTS (Collect Once, Use Numerous TimeS) to transform real-world data into actionable insights for translational research. The NEurOinformatics Network (NEON) applies this principle with neurology and national cohort use cases. METHODS/STUDY POPULATION: UNMC and Nebraska Medicine are deploying Data COUNTS to standardize data capture, ensure interoperability, and maximize reuse across research, clinical care, and operations. Teams integrate electronic health records, neuroimaging, biomarkers, wearable sensors, and social drivers of health into federated pipelines. HL7 FHIR and the OMOP Common Data Model maintain interoperability and reproducibility. Use cases include neurological disorders (multiple sclerosis, Alzheimer's disease, and Parkinson's disease), cancer outcomes through SEER, diabetes, and rural health disparities. Integration with the National Clinical Cohort Collaborative (N3C) leverages anchor variables and harmonized pipelines to connect local and national datasets for generalizable analytics and collaborative science. RESULTS/ANTICIPATED RESULTS: By linking with