and LPS dose. We then chose a minimum dose (500ug/kg) and time (3h) when multiple cytokines were elevated to measure lung injury scores using a point-counting technique on tissue sections stained with hematoxylin and eosin. The data are expressed as mean percentage of grid points lying within the peribronchial and superficial area in up to 20 fields. Percentage of peribronchial and superficial intrapulmonary hemorrhage, congestion, neutrophil infiltration and area of alveolar space were all assessed. RESULTS/ANTICIPATED RESULTS: Compared to the wildtype group (WT-G), the LPS-injected ACE2KO mice (LPS-G) exhibited a higher percentage of peribronchial intrapulmonary hemorrhage [(%): LPS-G, 10.56 ± 2.06 vs. WT-G, 5.59 ± 0.53; p DISCUSSION/SIGNIFICANCE: Establishing this novel mouse model of COVID-19 will facilitate studies investigating tissue-specific mechanisms of pathogenesis in this disease. This model can also be used to discover novel therapeutic targets and the design of clinical trials focusing on diagnostics, treatments and outcomes in COVID-19.

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A Phase 1 and Randomized Phase 2 Clinical Trial of Selinexor and Temozolomide in Recurrent Glioblastoma Among Adults: The Product of a Successful Team Science Approach

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OBJECTIVES/GOALS: Selinexor is a novel XPO1 inhibitor that blocks nuclear export, thus impairing DNA repair and causing apoptosis. Our goal was to conduct preclinical and clinical studies to test our hypothesis that selinexor's efficacy is boosted by priming with temozolomide and is associated with a tissue biomarker. METHODS/STUDY POPULATION: We leveraged a team science approach through the NCI Cancer Therapy Evaluation Program (CTEP) to design preclinical experiments, develop a novel RNAseq analysis pipeline, and use pre-existing clinical experience to open an early phase clinical trial for recurrent glioblastoma. Team members included a CTEP medical officer, cancer biologist, pharmacist, industry scientist, translational scientist, and early career clinician scientist mentored by an expert clinician scientist. Based on preclinical results, participants in the clinical trial experimental arm will receive sequential temozolomide 150mg/m2 on days 1-5 and a starting dose of selinexor 60mg on days 8 and 15 of a 28-day cycle. Participants in the control arm will receive monotherapy temozolomide. RESULTS/ANTICIPATED RESULTS: Sequential treatment of U87 cells and intracranial xenografts had superior DNA damage (É £H2A.X, cleaved PARP) and overall survival compared to combination or single-agent (HR 0.25 [95% CI, 0.07-0.84]; p=0.01, log-rank). We used the top-scoring gene pair method to identify an RNAseq signature associated with response to selinexor. We then designed a trial for first recurrent MGMT methylated glioblastoma. Primary objectives are safety and preliminary efficacy. Secondary objectives are overall response rate, efficacy, and validation of a molecular signature. Phase 1 dose finding (n=12) will be followed by a randomized phase 2 (n=72); using proportional hazards regression, RHR 0.5 with p DISCUSSION/SIGNIFICANCE: The NCI CTEP Project Team employs team science as a framework to successfully develop multidisciplinary collaborations, build investigator trial experience, and lead the way to future research opportunities. Our trial addresses a significant unmet need to offer novel therapies and molecular biomarkers in glioblastoma.

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Addressing complex and urgent problems through innovative team science: The University of Miami Laboratory for Integrative Knowledge (U-LINK)

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OBJECTIVES/GOALS: The goal of U-LINK is to bring together diverse scholars from multiple disciplines to address complex and challenging problems in healthcare, climate change, social equity, and community, through innovative team science, and aligned with the University of Miami's strategic plans. METHODS/STUDY POPULATION: The U-LINK program has supported developmental and implementation projects through a competitive selection process. Developmental funding was intended for teams to develop and refine ideas and to become established as an effective team. Additional funding was provided to teams to advance their projects by conducting data collection and feasibility testing. In addition, U-LINK has supported fellowship for pre-doctoral and affiliated doctoral trainees. Team science training was provided to all teams through didactic lectures and hands-on training. Teams were tracked longitudinally by using surveys and bibliometrics to measure success and impact including scholarly output and follow on funding. Network analysis was performed to analyze research collaboration networks before and after ULINK funding. RESULTS/ANTICIPATED RESULTS: U-LINK has funded pilot programs and initial phases for 57 projects and 13 fellowships in the last three years. Over 400 individuals on teams from 16 schools/academic units collaborated on these projects on topics such as resilience, climate change, social equity and societal challenges, health, and impact of recent legislation on LGBTQ+ community. While data collection and analysis are ongoing, initial results show successful outcomes from U-LINK projects including publications and $29.5m in follow-on external funding. We anticipate network analysis to demonstrate increased and continued multi-disciplinary collaborations among U-LINK teams through co-authorship networks and increase in collaborative grants being submitted and/or funded. DISCUSSION/SIGNIFICANCE: The University of Miami's U-LINK program has demonstrated success in forming interdisciplinary teams that have produced real-world solutions to complex problems by harnessing the inherent diversity and strength across UM's programs.

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An omega-6-derived eicosanoid negatively regulates platelet reactivity of cardiovascular patients at increased risk for thrombosis

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OBJECTIVES/GOALS: This study aimed to investigate the mechanistic effects of the omega-6-derived eicosanoid 12-HETrE on platelets of cardiovascular patients at risk for a recurrent cardiovascular event triggered by thrombosis. 12-HETrE negatively regulates platelet reactivity through binding to the prostacyclin receptor in platelets.

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METHODS/STUDY POPULATION: Healthy donors were recruited from the Ann Arbor community and the University of Michigan Medicine Center. Cardiovascular patients with elevated cardiovascular risk were recruited from the Cardiac Catheterization Laboratory at Michigan Medicine Hospital. All subjects were recruited under study protocols approved by the University of Michigan IRB. Healthy donors were matched with the cardiovascular patients regarding age, sex, race, and BMI. Whole blood was collected via venipuncture into vacutainers containing sodium citrate. Platelets were isolated via serial centrifugation and treated ex vivo with vehicle control, 12-HETrE, or Iloprost. RESULTS/ANTICIPATED RESULTS: Based on our previous studies, we chose to treat platelets ex vivo with 25uM of 12-HETrE for 10 minutes. Using platelets of healthy donors, we have shown that treatment with 25uM of 12-HETrE for 10 minutes inhibited platelet aggregation and activation, and activated protein kinase A, suggesting activation of the prostacyclin receptor. We conducted a preliminary study to demonstrate that ex vivo treatment of 12-HETrE regulated signaling pathways in platelets such as cell-to-cell interaction, platelet activation and cytoskeleton rearrangements. In this study, we have demonstrated that treatment with 12-HETrE regulated receptors and intraplatelet proteins in platelets of cardiovascular patients. Furthermore, these proteins are involved in critical pathways in the platelet. DISCUSSION/SIGNIFICANCE: Dual antiplatelet therapy has significantly decreased mortality due to thrombotic events. However, cardiovascular events triggered by thrombosis persist as the leading cause of death in the US. This study may uncover key regulators to be targeted for the long-term goal of providing additional protection to reduce future incidence of thrombosis.

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Clinical Translational Approach to Targeted Therapy in SLC6A1-related Neurodevelopmental Disorder

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OBJECTIVES/GOALS: SLC6A1-Related Neurodevelopmental Disorder (SLC6A1-NDD) is a leading genetic cause of epilepsy and autism. Haploinsufficiency of SLC6A1 leads to reduced uptake of GABA from the synaptic cleft, and increased extracellular GABA in mice. It is a candidate for gene transfer therapy, but translational read outs are needed. EEG is a promising biomarker. METHODS/STUDY POPULATION: The SLC6A1-NDD program includes a specialty clinic and prospective cohort study run in parallel with pre-clinical gene therapy development. Characterization and pre-clinical testing of a homozygous knock-out, heterozygous knock-out, and two humanized knock-in models are on-going, including EEG analyses before and after treatment. Patients with a confirmed diagnosis of SLC6A1-NDD are seen annually in a specialty clinic and a subset participate in the cohort study which collects standardized questionnaires, EEGs, and MR Spectroscopy to measure glutamate and GABA. Gene Therapy Program investigators meet weekly to discuss progress on pre-clinical and clinical trial readiness on SLC6A1-NDD and to align efforts on translational read outs, including EEG, in both humans and the pre-clinical models. RESULTS/ANTICIPATED RESULTS: We have enrolled the full cohort of 20 participants in the prospective SLC6A1-NDD cohort study. Preliminary results have shown that all but 1 individual has a history of developmental delay, and 8 of the 24 individuals in our clinical cohort had at least one episode of developmental regression. Over 90% have epilepsy, and 17/20 in the cohort study have intermittent rhythmic delta activity on EEG. The full knock out mice have behavioral and learning deficits and abnormal electrical brain activity on telemetry, including bursts of spike trains, analogous to epileptiform activity seen in humans. Next steps include quantitative analysis of both mouse and human EEG to develop a translational brain-based biomarker. We plan to assess delta power and investigate genotype-phenotype correlations in mice and humans. DISCUSSION/SIGNIFICANCE: With targeted therapies in development for SLC6A1-NDD, translational biomarkers that demonstrate engagement with the brain are critical. With clinical heterogeneity in SLC6A1-NDD, biomarkers can objectively capture change. Collaborative translational projects may improve efficiency in rare disease research to facilitate early phase trials.

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Datathon Revisited: Implementation of Lesson Learned

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OBJECTIVES/GOALS: In 2020, Baylor College of Medicine held a datathon to introduce a data warehouse, identify its capabilities/limitations, foster collaborations, and engage trainees. The event was held again in 2022, and lessons learned (e.g., tools for data self-service or team communication) were applied. METHODS/STUDY POPULATION: Senior faculty reviewed proposals with an emphasis on feasibility, impact, and relevance to quality improvement or population health. Selected teams worked with Information Technology (IT) for 2 months and presented findings at a 1-day event. Surveys were administered to participants before and after the event to evaluate their background, team characteristics, collaborations, knowledge before and after the datathon, perceived value of the datathon, and plans for future work. Descriptive statistics of respondents' self-reports were tabulated. RESULTS/ANTICIPATED RESULTS: In 2022, 19 of 36 projects were accepted (13/33 in 2020). At both events, most projects studied quality improvement or clinical outcomes. Of 82 participants in 2022, 54 completed surveys. In 2022, 72% had no datathon experience (48% in 2020). Median effort was 10 person-hours; median IT time was 20% (20 and 10%, in 2020). Seven respondents finished and 21 partially finished their projects (1 and 11, in 2020); 92% made new collaborations (91% in 2020). Respondents strongly agreed that: the experience was valuable (n=28), they would participate in future datathons (n=30), and they would use the warehouse for future work (n=25). Twenty-seven have planned abstracts; 25 have planned manuscripts. DISCUSSION/SIGNIFICANCE: The 2022 datathon had more participants with less experience, potentially due to improved promotion and training opportunities. Fewer person-hours and a higher percentage of IT time were required as compared to 2020, and more projects were completed, possibly due to increased IT efficiency.

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