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

Kimberly Goodspeed[1], Deepa Sirsi[2], Steven Gray[2], Matthew Rioux[2], WeiRui Guo[2], Susan Iannaccone[2]
[1]University of Texas Southwestern Medical Center [2]UT Southwestern Medical Center

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

Andrew J. Zimolzak[1], Katherine Sippel[1], Jessica A. Davila[1], Michael E. DeBakey[2], Vamshi Punugoti[1], Paul E. Klotman[1], Laura A. Petersen[1], Michael E. DeBakey[2], Gloria Liao[1], Lee Leiber[1], Christopher I. Amos[1]
[1]Baylor College of Medicine [2]Veterans Affairs Medical Center

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.

https://doi.org/10.1017/cts.2023.457 Published online by Cambridge University Press