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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Development of an Oncolytic Adenovirus to Treat Metastatic Colorectal Cancer

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OBJECTIVES/GOALS: Colorectal cancer (CRC) is a leading cause of cancer mortality, and many patients will develop metastatic disease at some point during their treatment course. Conventional therapies such as surgery, chemotherapy, and radiation are often of limited effectiveness in these advanced stages, which necessitates the development of novel therapies. METHODS/STUDY POPULATION: Our group has designed an oncolytic adenovirus backbone structure expressing the sodium iodide symporter (NIS) which can be used in conjunction with radioiodine to facilitate cancer imaging and therapy. Using multiple CRC cell lines, oncolytic adenoviruses with different fibers were tested in vitro to determine which of these modifications yielded the highest binding to the cancer cells. Additionally, multiple promoter structures are being tested to determine the impact on the replication and oncolytic effect of the virus. Furthermore, the potential of adenovirus-mediated NIS expression to facilitate PET/CT imaging and therapy with I-131 will be explored. RESULTS/ANTICIPATED RESULTS: The Ad5/3 chimeric fiber modification demonstrated the best binding in CRC cell lines. Additionally, tissue specific promoters are employed in oncolytic viruses to confer selective replication in cancer cells, while minimizing off target effects in nearby normal tissues. We have employed a Cox2 promoter, which has demonstrated an excellent oncolytic effect. In vitro NIS expression was shown in multiple CRC cell lines through immunostaining. Small animal PET/CT imaging demonstrated signal uptake in mice with subcutaneous CRC tumors after virus and radioiodine (I-124) administration. We anticipate that future studies employing radioactive iodine (I-131) in combination with our oncolytic virus will yield an augmented antitumor effect. DISCUSSION/SIGNIFICANCE: The NIS-expressing adenovirus has the ability to support radionuclide-based imaging and therapy for CRC. With additional pre-clinical testing, our adenovirus construct has the potential to bring NIS-based therapeutics to the bedside to positively impact CRC patient care outcomes.

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Eribulin Synergizes with STING Agonists by Enhancing Type 1 Interferon Expression and Improves Antitumor Efficacy as Combination Treatment

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OBJECTIVES/GOALS: Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks effective targeted treatment options. TNBC's greater degree of immunogenicity than other breast tumors makes immunotherapy a viable strategy. Strategies to improve the immunotherapy response includes targeting the cGAS-STING innate immune pathway with STING agonists. METHODS/STUDY POPULATION: We have previously shown in vitro that eribulin, a microtubule destabilizer currently used in the treatment of TNBC, functions as an indirect STING agonist because it promotes the release of mitochondrial DNA into the cytoplasm. Separately, eribulin also significantly enhances type I interferon expression induced by STING agonists measured by qRT-PCR through a second TBK1-dependent mechanism downstream of STING activation through detecting higher amounts of phosphorylated IRF-3 by western blot protein analysis. Mechanisms of eribulin-mediated interferon expression occur in immune and TNBC cells and are shared with other microtubule destabilizers but not with the microtubule stabilizing agent paclitaxel. RESULTS/ANTICIPATED RESULTS: We determine that the enhancement of type I interferon expression by eribulin is pharmacologically synergistic with multiple STING agonists. The significant enhancement by eribulin led us to evaluate the antitumor efficacy of eribulin in combination the STING agonist ADU-S100 in a challenging spontaneous mammary tumor model MMTV-PyVT. We show that the combination treatment significantly decreased tumor growth which allowed for longer survival compared to other groups. This is particularly interesting because of our previous studies showing that eribulin alone, but not paclitaxel, promotes the activation of CD4+ T-cells in the spleen and draining lymph nodes of BALB/c mice with 4T1 tumors through flow cytometric analysis. DISCUSSION/SIGNIFICANCE: These data contribute to accumulating evidence that there are important mechanistic differences between the microtubule targeted chemotherapeutics currently used in the treatment of TNBC and suggest that eribulin can act as an immune adjuvant in addition to its anti-mitotic effect.

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Etiology of Hepatocellular Carcinoma in the 27-County Rochester Epidemiology Project Catchment Area, 2010-2021

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OBJECTIVES/GOALS: The goal of this study is to examine the incidence, etiology, and outcomes of hepatocellular carcinoma (HCC) in a 27-county region in SE Minnesota and W Wisconsin between 2010 and 2021. A comparison of the first to second half of the period will be made to look for possible trends. METHODS/STUDY POPULATION: The Rochester Epidemiology Project (REP) is a database of patient records across SE Minnesota and W Wisconsin. Starting in 2010, the REP opened to a 27-county catchment area, which includes over 1.3 million patients with a population coverage of approximately 64%. This study will use the expanded REP data to collect data on patients 20 years of age and older with a new diagnosis of HCC between Jan 1, 2010 and Dec 31, 2021â€"an estimated 1000 cases. Patients with a record of less than one year of residence in the catchment area will be excluded. Data on etiology, comorbidities, and outcomes of HCC will be extracted from medical records and analyzed for risk factors and changes over time. RESULTS/ANTICIPATED RESULTS: We anticipate that the overall incidence of HCC in the REP geographic area has increased over the period of 2010 to 2021. We anticipate that the prevalence of hepatitis C virus infection in patients with HCC has between 2010 and 2021, due to the widespread use and accessibility of hepatitis C-specific antiviral treatment over the past decade. We anticipate that the prevalence of NAFLD in patients with HCC has increased between 2010 and 2021. We do not anticipate significant changes in treatment modality or survival outcomes over this period. DISCUSSION/SIGNIFICANCE: This study will provide a comprehensive update on the state, etiology, and outcomes of HCC in the area surrounding

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