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Increasing access to basic team science concepts through asynchronous online modules: Team science 101

Jennifer Molano[1], Laura Hildreth[1], Anna Johns[1], Elizabeth J Kopras[1], Angela Mendell[1], Rebecca C. Lee[1], Stacey Gomes[2], Megan Johnstone[1], Jackie Knapke[1], Jack Kues[1] and Jason T. Blackard[1]
[1]University of Cincinnati and [2]Cincinnati Children's Hospital Medical Center

OBJECTIVES/GOALS: Team science (TS) competency is important for translational science team collaboration. However, there are few educators available to assist teams. Asynchronous learning is an effective strategy for delivering TS content. The goal of this project is to expand TS education by providing online access to our learners using online modules. METHODS/STUDY POPULATION: The Collaboration and Team Science (CaTS) team at the University of Cincinnati provides a robust TS education and training program. As the need for team science gains recognition, CaTS has received increased requests for services, leading to a need to broaden TS offerings. To address this demand, the CaTS team created "Team Science 101," an online, asynchronous, series of 15 modules covering basic team science concepts. Each module consists of an educational recording lasting an average of 20 minutes, optional topic resources, pre- and post-module surveys assessing learners' confidence and satisfaction, post-module knowledge checks, and evaluation questions. Upon completing all modules, participants receive a completion certificate. RESULTS/ANTICIPATED RESULTS: TS 101 will be piloted with a group of participants who expressed interest in asynchronous TS content and will be adjusted based on the feedback received. The associated pre- and post-module survey, post-module knowledge check, and evaluation questions will be monitored to determine learning levels and improve TS 101 overall. Canvas is the educational platform that houses these modules, allowing for participant follow-up and scalable dissemination. The CaTS team plans to disseminate TS 101 nationally and internationally for anyone interested in this resource. DISCUSSION/SIGNIFICANCE OF IMPACT: There is a national effort to collect and curate TS education, training, and toolkits. TS 101 will be a useful educational tool that will expand the reach of team science educators, provide the foundation for educators to explore topics more deeply by building on the module topics, and provide education to broader audiences who lack access to TS experts.

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Tracking newly regenerated oligodendrocytes in a preclinical mouse model of multiple sclerosis

Zeeba Manavi[1,2], Lauren Rosko[3], George Melchor[3], Maryna Baydyuk[2] and Jeffrey Huang[2,3]
[1]Georgetown-Howard Universities Center for Translation Science; [2]Departments of Biology, Laboratory of Neuroinflammation and Glia Biology, Georgetown University, Washington and [3]Interdisciplinary Program in Neuroscience, Georgetown University, Washington

OBJECTIVES/GOALS: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that affects 2 million people worldwide causing severe disability. This study uses the Gamt-GFP transgenic mouse line as a novel approach to track oligodendrocyte lineage cell regeneration in inflammatory demyelination for identifying potential therapies. METHODS/STUDY POPULATION: We previously showed that Gamt, an enzyme required for creatine synthesis, is essential for oligodendrocyte (OL) maturation and survival using the Gamt-Green Fluorescent Protein (Gamt-GFP) reporter line. In this study, we capitalize on this finding and track OL lineage cells in an experimental autoimmune encephalomyelitis (EAE) mouse model by inducing immune-mediated demyelination in the Gamt-GFP reporter line. At 7 days post-immunization (dpi), both control and EAE mice receive 4 mg/kg tamoxifen for 4 consecutive days to induce GFP expression. GFP+ cells and those also expressing OL lineage markers [Olig2 (pan-OL lineage cell marker), NG2 (OL precursor cells; OPCs), and CC1 (mature OL)] are quantitated by immunofluorescent staining of spinal cord sections collected at 28 dpi. RESULTS/ANTICIPATED RESULTS: Preliminary data using immunofluorescent staining demonstrated GFP was expressed in Olig2+ cells in the inflammatory ventral white matter lesions of mice with EAE, whereas no GFP labeling was present in the control mice. Moreover, GFP+ cells also expressed NG2+. In contrast, few CC1 + cells were detected in the inflammatory lesions. The low number of dual labeled GFP+CC1+ cells in these lesions suggests OPCs under the EAE environment are unable to efficiently differentiate into mature OL. Therefore, the Gamt-GFP reporter mouse can be used to identify and track activated OL lineage cell populations (i.e., GFP+CC1) in inflammatory lesions in the EAE mouse model. DISCUSSION/SIGNIFICANCE OF IMPACT: The Gamt-GFP reporter line identifies activated OL lineage cells responding to inflammatory demyelination, making it a valuable tool for testing potential therapeutics aimed at enhancing remyelination. This model helps bridge the gap between preclinical and clinical research to guide MS therapy development.

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Is PHASTR faster? A target trial emulation case study in the N3C

Steve Johnson[1], Carolyn Bramante[2], Til Stürmer[3], John Buse[4], Talia Wiggen[5], Jared Huling[6] and Andrew Toler[7]
[1]University of Minnesota; [2]Division of General Internal Medicine, Department of Medicine, University of MN Medical School; [3]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill; [4]Division of Endocrinology, School of Medicine, Department of Medicine, University of North Carolina Chapel Hill; [5]Institute for Health Informatics, University of Minnesota, Minneapolis; [6]Division of Biostatistics and Health Data Science, School of Public Health David Sahner, University of Minnesota and [7]NCATS contractor (Axle Informatics)

OBJECTIVES/GOALS: Our study team won a Public Health Answers to Speed Tractable Results (PHASTR) contract to conduct a target trial emulation to answer "Does metformin show a reduction of severe outcomes of COVID-19 or of Long COVID in the N3C Data Enclave?" We quickly delivered an answer due to productive technical and collaboration support in the N3C. METHODS/

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STUDY POPULATION: Our analytic plan was updated based on helpful feedback from the PHASTR program. We performed a trial emulation analysis using the N3C data, comparing adult new users of metformin to controls prescribed fluvoxamine, fluticasone, ivermectin, or montelukast. The composite outcome was Long COVID or Death (LC/D) within 180 days of COVID infection. We used entropy balancing to estimate the average treatment effect with a weighted log-linear model. Productivity was enhanced by reusing code workbooks and validated codesets from related N3C projects. The team of 4 (physician, informaticist, data programmer, and statistician) and key unpaid advisors spent 10 weeks developing and analyzing the data. RESULTS/ANTICIPATED RESULTS: Totally, 9,660 patients were identified for analysis. After weighting, there were 248 in the metformin and control groups. In the metformin group, 4.0% developed LC/D vs. 8.5% in the control group, with an adjusted risk ratio (aRR) of 0.47 (95% CI 0.25 to 0.89). Results were consistent across subgroups and sensitivity analyses. The PHASTR contract structure helped produce high-quality results quickly by not only providing funding but also requiring a compressed timeline for a small team to focus on the study. The most time was spent on contract execution, enclave provisioning, and too many last-minute download requests. A project final report was submitted in March and a full manuscript was submitted in September. DISCUSSION/SIGNIFICANCE OF IMPACT: The analysis was productive because the environment made reuse easy and supported rich collaborations among clinicians, informaticists, epidemiologists, statisticians, and data developers. Advice from PHASTR advisors (Axel) and N3C diabetes domain team members was also key to a faster completion.

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Becoming multilingual in thought languages

Colin Hoffman[1], Mary Bevilacqua[2] and Brian Weaver[3]
[1]Colorado State University; [2]University of Colorado and [3]Community College of Denver

OBJECTIVES/GOALS: Understanding cognitive habits and values of individuals or groups, and providing tools to apply them to collaborative, interdisciplinary endeavors to better communicate between different industries, functions, and cultures. METHODS/STUDY POPULATION: Using literary research to establish groupings of common core values in interpersonal communications, applying established 5 patterns of "thought languages" to scale to group communications. Accepted psychological personality inventories for individuals will overlay into cognitive values, primarily using the current big five OCEAN model. Demonstrating these values to find common goals among interdisciplinary collaborations can identify prospective members, cultural differences in industry, patient communication, and public messaging in STEM. Integrating these tools into research groups to establish more efficacious communication between teams, governing bodies, and patient communication can be sampled via pre and post research surveys of feeling understood. RESULTS/ANTICIPATED RESULTS: The results of feeling understood by various parties in collaborative research would be a measure of not just effective expressed communication, but received communication. Feeling understood is a current metric of communication that is correlated with satisfaction, trust, and interdependence. All of these results are integral to the successful operations of collaborative projects. Demonstrating a positive correlation between applying the 5 thought languages and better-surveyed outcomes of understanding will guide the effectiveness of this as a future collaborative tool for translational sciences. DISCUSSION/SIGNIFICANCE OF IMPACT: The significance of effective communication based on positive reception will foster future collaborations. Encouraging familiarity between differing individuals, groups, and industries, even between subjects and researchers, patients and healthcare. More satisfaction, more trust, and more interdependence will propagate between these groups.

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Neutrophils propagate inflammation and fibrosis in primary sclerosing cholangitis

Abid Anwar, Sofia Jerez Ortega, Maleeha Kalaiger, Kaitlin Friesland, Jordan Young, Amaury E. Tuerlinckx, Usman Yaqoob, Robert C. Huebert and Nidhi Jalan-Sakrikar
Mayo Clinic, Rochester

OBJECTIVES/GOALS: Primary sclerosing cholangitis (PSC) manifests with an inflammatory milieu that leads to fibrotic scarring of the liver. Human PSC liver bile ducts are enriched with neutrophils; however, their infiltration and functional role is unexplored. Our goal is to investigate the mechanism and impact of peribiliary neutrophil infiltration observed in PSC. METHODS/STUDY POPULATION: Primary cholangiocytes (bile duct cells) isolated from WT and mouse models of PSC (3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)-fed mice and Mdr2-/- mice) were analyzed by RNA-sequencing. Immunofluorescence (IF) was performed on liver tissues from PSC patients and mouse models of PSC for markers of bile ducts and neutrophils (KRT19 and MPO). Intrahepatic leukocytes (IHL) isolated from mice livers were evaluated for neutrophil abundance and activation state. Anti-Ly6G antibody-mediated neutrophil depletion in Mdr2-/- mice was analyzed by IF, histology, and cytometry by time-of-flight (CyTOF). Cholangiocytes stimulated with TNFα (to induce an inflammatory phenotype) were analyzed for neutrophil chemoattractants with genetic and pharmacological interventions. RESULTS/ANTICIPATED RESULTS: RNA-seq analysis of primary cholangiocytes from PSC mouse models revealed enrichment in inflammatory and neutrophil degranulation pathways. Flow cytometry and RT-PCR analysis revealed an increase in the neutrophil population in PSC mice with activated phenotype. Peripheral depletion of neutrophils in Mdr2-/- mice alleviated liver injury and inflammation, along with a reduction in peribiliary neutrophil infiltration and attenuated bridging fibrosis. CyTOF analysis showed a significant reduction in CD8+ T cells upon neutrophil depletion, implying neutrophils sustain CD8+ T cells in PSC liver. Mechanistically in cholangiocytes, TNFα mediates expression of neutrophil chemoattractants, CXCL1 and CXCL8, through the cyclic GMP-AMP synthase stimulator of interferon genes (cGAS-STING) pathway. DISCUSSION/SIGNIFICANCE OF IMPACT: Our findings suggest that activation of the STING pathway in cholangiocytes in cholestatic liver disease triggers an immune response resulting in peri-portal neutrophil infiltration via CXC chemokines. The sustained presence of these activated neutrophils engages the adaptive immune system to perpetuate the inflammation and fibrosis seen in PSC.

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