METHODS/STUDY POPULATION: We searched PubMed, CINAHL, and SCOPUS through September 15, 2024, using keywords and appropriate subject headings related to AD, fluid biomarkers, and sleep. The search was developed and conducted in collaboration with a medical librarian. We also searched Google Scholar and screened the reference lists of relevant reviews. Two independent reviewers screened 1,657 peer-reviewed articles, of which 21 met the inclusion criteria (14 with biomarkers measured in cerebrospinal fluid [CSF] and 7 in blood). Two review authors independently extracted study details from included articles using a standardized data extraction template. RESULTS/ANTICIPATED RESULTS: Sample sizes ranged from 18 to 4,712 participants. Sleep duration was assessed using self-reported measures in 8 studies and objective measures in 13. For the 14 studies using CSF biomarkers, lower Aβ42 (3/14), Aβ40 (1/14), or the ratio (1/14) were associated with either short or long sleep duration; t-tau (3/14) and p-tau181 (4/14) levels were mostly associated with short sleep. For the 7 blood-based biomarker studies, Aβ42 (2/7), Aβ40 (2/7), and the ratio (3/7) had mixed results with either short or long sleep. T-tau (1/7) and p-tau181 (1/7) levels were associated with long sleep; NfL (2/7) was associated with both short and long sleep. Six studies reported nonlinear relationships, with both short and long sleep associated with unfavorable biomarker profiles. None of the studies investigated p-tau 217 or GFAP. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results suggest that the relationship between sleep duration and AD fluid biomarkers is very complex, and it highlights the importance of sleep in AD risk assessment and prevention. The inconsistency in findings stresses the need for standardized study design and measurement methods to clarify causality and inform clinical guidelines.

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Targeting negative-self-referential processing with transcranial magnetic stimulation: Feasibility studies

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OBJECTIVES/GOALS: Neuromodulation strategies like transcranial magnetic stimulation (TMS) can target specific neural circuits underlying particular psychiatric symptoms, potentially 1) enhancing understanding of mechanisms of illness and recovery and 2) acting as novel therapeutics. These feasibility studies lay foundation for a study of major depression. METHODS/STUDY POPULATION: Four healthy volunteers completed structural and functional MRI (fMRI). fMRI included a trait-adjective task, a negative self-referential processing task known to activate VMPFC, which is known to be abnormal in major depression. During the task, participants respond on a task pad whether they feel that each of a series of displayed adjectives (positive, negative, or neutral) applies to them. Three participants then participated in a simulated image-guided TMS session using their MRI data to target their VMPFC. Three-dimensional tracking of the participant's head and the TMS coil was used to position the coil for peak stimulation of the targeted brain region. RESULTS/ANTICIPATED RESULTS: Our team collected quality neural and behavioral data on the fMRI task; participants reported a tolerable experience. Simulated neuronavigated TMS showed feasibility and tolerability of positioning the device to stimulate VMPFC. The fMRI task activated the VMPFC as predicted. The MRI and TMS protocols were replicable and tolerable. These procedures can now be used experimentally by our team with confidence to test our hypothesis that targeting the VMPFC within the brain's default-mode network may normalize aberrant VMPFC activity seen in major depression, thereby improving excessive negative self-referential processing. DISCUSSION/SIGNIFICANCE OF IMPACT: This project lays essential groundwork for my K12 project, "Targeting Negative-Self Referential Processing in Depression with TMS," a longitudinal neuroimaging and behavioral study using these methods in the study population of people with major depression.

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Follicle-stimulating hormone is reduced following a novel nutritional therapeutic in postmenopausal women with obesity

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OBJECTIVES/GOALS: Increased follicle-stimulating hormone (FSH) is linked to declines in ovarian and metabolic function in older women. Obesity is both a manifestation and a driver of aging pathologies. In animal models, FSH and insulin resistance (IR) were reduced after 6 mos. of a nutritional therapeutic (GLYLO). Our goal was to translate preclinical evidence to humans. METHODS/STUDY POPULATION: An integrated, precision medicine approach identified a unique phenotype of aging-related debility relative to older females. A non-comparer pilot study was conducted to translate GLYLO preclinical findings to postmenopausal women with obesity (n = 85; >55 years; body mass index [BMI] = 35.0 ±4.35; range: 30.3–42.8). Participants meeting the inclusion and exclusion criteria (n = 13) were enrolled and received two capsules of GLYLO (vitamins and natural products) daily for 6 mos. Assessments for FSH, estradiol (E2), IR (homeostatic model [HOMA-IR]), total cholesterol (TC), low- (LDL), high-density lipoproteins (HDL), safety biomarkers (e.g., red cell distribution width [RDW%], mean corpuscular volume [MCV]), and depression (Center for Epidemiologic Studies Depression Scale) were conducted prior to and after 6 mos. RESULTS/ANTICIPATED RESULTS: Mixed-effect models with intent-to-treat analysis were applied to compare outcomes prior to (n = 13) and following (n = 7) the intervention. Significant reductions in FSH were observed (-13.1 [2.47] Δ/SD; p = 0.002)) following the 6-month intervention. Interestingly, BMI, E2 (p = 0.412), HOMA-IR (p = 0.885), TC (p = 0.363), and LDL (p = 0.145) were unchanged, while HDL

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decreased significantly (-9.7 [3.82] Δ/SD; p = 0.044). Other biomarkers, RDW% (-0.2 [0.05] Δ/SD; p = 0.009) and MCV (-2.3 [0.33] Δ/SD; p = 0004), were significantly reduced. All other safety parameters were not altered. Six participants reported mild to moderate adverse events (acid indigestion) and were lost to follow-up. Depression scores significantly increased (+4.0 [0.75] Δ/SD; p = 0.002)). Results were similar with and without intent to treat analysis. DISCUSSION/SIGNIFICANCE OF IMPACT: Decreased FSH, but not IR, was observed following six months of GLYLO in postmenopausal women with obesity. Significant alterations in HDL, depression, RDW%, and MCV warrant further investigation. Findings are limited by the small sample size and loss to follow-up. Randomized, controlled trials are needed to confirm these results.

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Modeling of cancer mutations found in pediatric DICER1 syndrome informs novel therapeutic targeting strategies

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OBJECTIVES/GOALS: Large-scale tumor sequencing efforts have led to annotations of novel cancer hotspot mutations that may underlie driver or cooperative function. We have sought to define the molecular consequences of such hotspots associated with pediatric DICER1 syndrome cancers, with the ultimate goal of revealing novel targets that may inform new standards of care. METHODS/STUDY POPULATION: We have performed genomic analysis to identify tumor types (in TCGA and MSK-IMPACT patient data) for which mutations in the Dicer1 gene (encoding Dicer protein) emerge as the dominant signature of driver function. As Dicer is a critical RNA processing factor responsible for the generation of microRNAs, which are posttranscriptional gene regulatory molecules, we have modeled these mutations in human embryonic stem cells in order to study the direct effects on miRNAs and their target genes in an isogenic background. In addition to providing the required setting for unambiguous attribution of function to specific mutations, clonal human ES cells offer an opportunity for modeling of both developmental and cancer requirements associated with altered Dicer function. RESULTS/ANTICIPATED RESULTS: Through generation of genomics and functional datasets from matched genotypes in Dicer mutated human ES cells, we have identified specific alterations in miRNAs and their effects on target genes. Unexpectedly, we found direct evidence for both loss of function and gain of function attributable to Dicer mutations. In addition, through integrated analysis of genomic data from tumor sequencing datasets and our human ES cell models, we have identified potential miRNA and target gene alterations that underlie tumorigenic potential, nominating gene candidates for targeted therapy in DICER1 syndrome. Direct mouse modeling of such candidate gene targets has revealed evidence for driver function of identified miRNA and their targets. DISCUSSION/SIGNIFICANCE OF IMPACT: DICER1 syndrome cancers comprise a wide variety of rare pediatric tumor types. Presently, we still lack an effective standard of care. Furthermore, the previous lack of molecular profiling precluded targeted therapy opportunities. Our precise knock-in modeling of Dicer hotspots and deep profiling of relevant tumors now provide candidate targets.

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Staphylococcus colonization drives IFN-mediated monocyte recruitment and skin barrier disruption in cutaneous lupus erythematosus lesions

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OBJECTIVES/GOALS: Cutaneous lupus erythematosus (CLE) is an inflammatory skin manifestation of lupus. CLE lesions are frequently colonized by *Staphylococcus aureus*, a microbe known to promote IFN production and inflammation. Here, we investigate whether type I IFN and inflammatory gene signatures in CLE lesions can be modulated with a topical antibiotic treatment. METHODS/STUDY POPULATION: SLE patients with active CLE lesions (n = 12) were recruited and randomized into a week of topical treatment with either 2% mupirocin or petroleum jelly vehicle. Paired samples were collected before and after 7 days of treatment to assess microbial lesional skin responses. Microbial samples from nares and lesional skin were used to determine baseline and posttreatment *Staphylococcus* abundance and microbial community profiles by 16S rRNA gene sequencing. Inflammatory responses were evaluated by bulk RNA sequencing of lesional skin biopsies. Immunophenotyping of CLE lesions was performed using CIBERSORTx to deconvolute the RNA-seq data into predicted cell populations impacted by treatment. RESULTS/ANTICIPATED RESULTS: We identified 173 differentially expressed genes in CLE lesions after topical mupirocin treatment. Mupirocin treatment decreased the abundance of *Staphylococcus* associated with CLE lesions without altering the overall diversity of the skin microbiota relative to vehicle. Decreased lesional *Staphylococcus* burden correlated with decreased IFN pathway signaling and inflammatory gene expression and increased barrier dysfunction. Interestingly, mupirocin treatment lowered skin monocyte levels, and this mupirocin-associated depletion of monocytes correlated with decreased inflammatory gene expression. DISCUSSION/SIGNIFICANCE OF IMPACT: Mupirocin treatment decreased lesional *Staphylococcus* burden and this correlated with decreased IFN signaling and inflammatory gene expression. This study suggests a topical antibiotic could be employed to decrease lupus skin inflammation and type I IFN responses by reducing *Staphylococcus* colonization.

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Investigating the impact of hematopoietic cell transplant on morbidity and mortality of children with sickle cell disease*

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OBJECTIVES/GOALS: Our main objective was to compare 5-year survival and organ function between patients with sickle cell disease (SCD) who underwent hematopoietic cell transplant (HCT) and those who did not undergo HCT. We hypothesized that organ function would be improved in those with SCD who underwent HCT when compared to those who remained on standard therapy.

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