Using 5-Azacitidine

Leukemia (T-LGLL) and Provides a Therapeutic Approach

Pathogenesis of T-Cell Large Granular Lymphocytic

Promoter Induces IL-15 Expression, Drives the

Mansour3, Monique Mathe-Allainmat4, Agnes Quemener5 and

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volume and both global (Spearman rank correlation coefficient

0.72, p=0.03) between ABC/2, the traditional ICH volume measuring approach, and our semi-automatic segmentation tool, with ABC/2 tending to overestimate ICH volume. There was an average of -6.51% of total brain volume loss with respect to initial brain volume at follow-up. There was a negative correlation between ICH volume and both global (Spearman rank correlation coefficient (R)=0.714, p=0.0044) and local atrophy (R=-0.785, p=0.0009), meaning that as ICH volume increases, there is greater brain volume loss. DISCUSSION/SIGNIFICANCE OF FINDINGS: Greater ICH volume is associated with greater brain volume loss both ipsilaterally, reflected as encephalomalacia, and globally. These findings are important as encephalomalacia can result in focal neurologic deficit and other neurological symptoms over time, while global brain atrophy is associated with dementia and cognitive decline.

Clinical Trial

Reversible DNA Hypermethylation of the Interleukin-15 Promoter Induces IL-15 Expression, Drives the Pathogenesis of T-Cell Large Granular Lymphocytic Leukemia (T-LGLL) and Provides a Therapeutic Approach Using 5-Azacitidine

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ABSTRACT IMPACT: This work describes, for the first time, the methylation in patients with T-LGLL, focusing on the IL-15 promoter, and clearly demonstrates that 5-azacitidine decreases IL-15 production leading to T-LGLL cell death. These results form the basis a translational clinical trial in T-LGLL that will begin accrual in 2021

OBJECTIVES/GOALS: T-LGLL is an incurable leukemia with few treatment options driven by overexpression of IL-15. Our objective is to characterize the methylation status of the IL-15 promoter in T-LGLL patients and evaluate the potential use of 5-azacitidine (5-aza) in a translational trial by studying the effect of 5-aza in vitro on IL-15 levels, and the IL-15 promoter. METHODS/STUDY POPULATION: We sorted T-LGLL patient (n=3) and normal donor (ND) samples (n=3) for CD3+/CD8+/CD5-/dim for T-LGLL immunophenotype. We analyzed DNA methylation and gene expression profiling using reduced representation bisulfite and RNA sequencing and determined differential methylation and gene expression using 1-way ANOVA analysis. To determine the functional significance of differential methylation, we evaluated MOTN-1 T-LGLL cell viability in vitro with 5-aza at increasing concentrations. Next, we evaluated IL-15 gene expression in MOTN-1 cells treated with 5-Aza versus MOTN-1 with control using western immunoblot. Finally, we exposed MOTN-1 cells to a novel IL-15 inhibitor, IBI-15, and compared cell viability against MOTN-1 cells exposed to an inactive control. RESULTS/ANTICIPATED RESULTS: There was significant differential methylation (P=0.0178) and expression (P=0.0059) in T-LGLL patients vs ND. These data revealed significant differential hypermethylation of gene promoters, including an increase in DNA methylation of the IL-15 promoter in T-LGLL cells vs ND. In MOTN-1 cells treated in vitro with 5-Aza at 24 and 48 hours, a dose-dependent decrease in the viability of T-LGLL cells was observed, from 100% to 49.5%, p=0.037. Further, a marked decrease in IL-15 expression was observed at all concentrations of 5-aza compared to control (p=0.0001). Finally, a decrease in cell viability was observed utilizing the IL-15 inhibitor IBI-15 vs control. These results confirm that 5-aza leads to decreased transcription of the IL-15 gene, possibly due to hypomethylation of the IL-15 promoter. DISCUSSION/SIGNIFICANCE OF FINDINGS: Hypermethylation of the IL-15 promoter and subsequent increase in IL-15 is critical to the pathogenesis of T-LGLL. Inhibition of the IL-15 promoter by 5-aza leads to down-regulation of the IL-15 gene transcript, which is sufficient to induce T-LGLL cell death. Based on these results, a phase I trial will be conducted using CC-486 (oral 5-Aza) in T-LGLL.

Data Science/Biostatistics/Informatics

Electrical stimulation of hippocampus and amygdala produces multiple distinct responses in human ventral temporal cortex

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ABSTRACT IMPACT: This study characterizes interactions between human limbic circuitry and ventral temporal cortex using single pulse electrical stimulation, which may inform emerging stimulation therapies for epilepsy. OBJECTIVES/GOALS: The goal of electrical brain stimulation treatment is to modulate brain network function. However, stimulation inputs to different brain sites alter the network in a variety of ways. This study examines that variability by characterizing responses in a target region while stimulating multiple other brain sites. METHODS/STUDY POPULATION: We measured voltages in intracranial EEG in 6 patients who had electrodes implanted for epilepsy monitoring. We stimulated pairs of electrodes at multiple sites in the brain with a single pulse every 5 to 7 s and measured the resulting corticocortical evoked potential (CCEP) responses in the ventral temporal cortex (VTC). Using a novel clustering method, we uncovered sets of distinct canonical

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response shapes from the 20 to 500 ms post-stimulation period. This allowed us to group stimulation sites that evoked similar responses. We then related each group to high frequency, broadband, changes in spectral power as a reflection of local neuronal activity. RESULTS/ANTICIPATED RESULTS: We found that the VTC receives strong inputs specifically from the amygdala and hippocampus, both in terms of amplitude and broadband spectral power change. However, inputs from the hippocampus produced a different canonical shape than those from the amygdala. We also observed that VTC responses to inputs from the insula clustered in shape with those from the amygdala. These clustering patterns were consistent across subjects, although the actual shapes of the clusters showed variability. We further observed that some shapes were more associated with increases in overall neuronal activity than others, as reflected by broadband spectral power change. DISCUSSION/SIGNIFICANCE OF FINDINGS: Stimulation of connected sites may drive excitability at the target region in ways that are described by sets of full-time-course responses. By capturing their shapes, we can begin to decipher canonical input types at the circuit level. This approach might identify how stimulation inputs can be tailored to therapy while mitigating adverse effects.

**High Screening Efficacy Using Wearable Seismocardiography to Identify Aortic Valve Disease Patients, Potential to Tailor MRI Exams to Patient Needs**

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ABSTRACT IMPACT: A single seismocardiography (SCG) parameter has been shown to accurately classify aortic valve disease (AVD) status in healthy controls and AVD patients. This could support development of SCG as a quick, inexpensive screening tool to better tailor MRI examination to patients’ needs. OBJECTIVES/GOALS: MRI is used commonly for monitoring of aortic valve disease (AVD), but it has high costs. We hypothesize that energy in scismocardiograms (SCG) reflected by broadband spectral power change. DISCUSSION/SIGNIFICANCE OF FINDINGS: A high potential screening efficacy was observed using a single, linear SCG metric to identify AVD patients with flow abnormalities. If used to complement MRI surveillance protocols for AVD, this method has potential to serve as a quick, inexpensive tool for better tailoring MRI exams to patient needs.

**Dissemination and Implementation**

**Asymptomatic Thoracic Aortic Aneurysm Growth Rates and Predicting Factors: A Systematic Review and Meta-Analysis**

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ABSTRACT IMPACT: Through conducting this systematic review and meta-analysis, we will elucidate which factors influence thoracic aortic aneurysm growth, which will further help clinicians to properly stratify and manage their patients with TAAs. OBJECTIVES/GOALS: Thoracic aortic aneurysms (TAA) are an indolent but fatal disease, and the patient characteristics that predict both overall growth and growth rate are still not well characterized. Our goal is to conduct a systematic review and meta-analysis in order to better describe different patient characteristics that predict TAA growth. METHODS/STUDY POPULATION: M.M. conducted a search of Ovid MEDLINE, Embase, and Scopus to identify articles. Inclusion criteria were any longitudinal study reporting asymptomatic TAA growth, growth rates, or clinical proxies for growth such as dissection, rupture, emergency surgery, and death. M.H and P.B. independently applied the criteria to the results of the search. Conflicts were resolved by N.B. Data was extracted and risk of bias assessed independently by M.H. and P.B. Summary estimates of the outcome variables are combined across studies using standard meta-analysis methods. Heterogeneity is assessed via forest plots, chi2 test (Q test), and I2 statistic. Sensitivity analysis is conducted to assess robustness of the findings. RESULTS/ANTICIPATED RESULTS: The literature search resulted in 3,419 abstracts, of which 176 were included and thus require a full text review. Cohen’s Kappa coefficient was 0.64, indicating substantial agreement and high inter-rater reliability. We describe four categories of patient characteristics influencing the growth of asymptomatic TAAs: demographics, genetic or inheritable conditions, hemodynamic or biomechanical factors, and serum biomarkers. We describe the measure of effect for all variables. We anticipate there is a significant level of heterogeneity between studies, and potentially moderate risk of bias for many of the included studies as they are retrospective and observational in nature. Furthermore, we anticipate publication bias and evaluate...