mouse pancreas for in vivo studies. As a second approach, recombinant wild-type or engineered CXCL12 monomer or dimer proteins were applied to cells in culture or administered intra-peritoneal to study the effects on tumor growth. RESULTS/ANTICIPATED RESULTS: Mice engrafted with CXCL12-expressing cells had a better survival rate, delayed tumor growth and smaller tumors. Tumors from these mice had significantly less proliferation, measured by Ki-67 staining. In vitro analysis of CXCL12-expressing cells showed decreased viability and growth rates. Percent of cells in the cell cycle G2 phase was also decreased, suggesting cell cycle progression blockade. Viability of human PDAC cells dose-dependently declined upon wild-type CXCL12 treatment, with the non-motile dimer-dominant dose (1000 nM) exhibiting maximal effect. Treatment in an allogeneic mouse model of PDAC with locked-dimer CXCL12, but not wild-type, reduced tumor burden. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results support the notion that biased CXCL12 signaling may be therapeutically exploited to limit pancreatic cancer progression.

2070

High-intensity focused ultrasound (HIFU) can be used synergistically with tamoxifen to overcome resistance in preclinical and patient derived xenograft models

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OBJECTIVES/SPECIFIC AIMS: The goal of this study is to evaluate a potential strategy to overcome tamoxifen (tam) resistance by using tam in combination with high-intensity focused ultrasound (HIFU). Tam is the most commonly used anti-cancer therapeutic agent in estrogen receptor positive (ER+) breast cancer (BC) which accounts for ~70% of BC cases. Tam treatment decreases a woman's risk of recurrence by 50%; however, BC that is initially responsive to tam often develops resistance. METHODS/STUDY POPULATION: HIFU deposits acoustic energy locally to a cancerous region, which induces strong vibrations of molecules inside and outside of the cells. The resulting absorption causes rapid heating and mechanical disruption. This clinically relevant, noninvasive, and nonionizing physical force modality, has been shown to synergistically enhance chemical anticancer therapies. RESULTS/ANTICIPATED RESULTS: In this study we found that treatment of MCF7 cells with HIFU and tam has additive antiproliferative effects and mediates increased cell death. Additionally, we used tam resistant (TR) MCF7 cells that had been exposed to low-dose tam over time until they acquired resistance. When MCF7 TR are treated with tam there is no change in viability; however, treatment with HIFU in combination with tam decreased viability of both MCF7 and MCF7 TR to 19% and the viability of the cell lines was indistinguishable. We next evaluated the effect on MCF7 Y537S mutant ESR1, where ER is mutated to be constitutively active. Treatment of MCF7 Y537S had no significant decrease in viability of combination therapy compared with viability after HIFU alone. Analysis of ERalpha gene expression showed that HIFU treatment increased ERalpha expression in MCF7 TR cells, thus resensitizing these cells to tam and allowing these therapies to work synergistically. Our team developed a system to evaluate the potential of this combination of therapies in a patient-derived xenografts (PDX) model. PDX have emerged as a novel translational tool for cancer research with the potential to more accurately recapitulate the molecular and behavioral aspects of cancer. The WHIM20 PDX is a tamoxifen resistant tumor where the patient developed the Y537S mutation in ESR1. Ex vivo experiments on PDX tumor pieces demonstrated that combination therapy of HIFU and tam work synergistically to increase cell death of these tumors. Further, cryogenic-scanning electron microscopy was utilized to directly demonstrate the physical disruption to both cellular and tumor microenvironment post exposure to combination treatment. DISCUSSION/SIGNIFICANCE OF IMPACT: These studies present a novel translational strategy to overcome tamoxifen resistance in ER+ BC.

2459

Hippocampal network disruption in early amyloid pathology

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OBJECTIVES/SPECIFIC AIMS: We aim to show that amyloid accumulation in an animal model of Alzheimer's disease leads to a preferential disruption of inhibitory parvalbumin-expressing interneurons, and the peri-neuronal nets that surround them, resulting in downstream network alterations to potentially explain early mechanisms of memory impairment in the disease. METHODS/STUDY POPULATION: We employ the 5xFAD mouse model of familial Alzheimer's disease crossed with transgenic mouse lines which fluoresce red or green in specific neuronal populations. We conducted immunostaining and immunoblotting in amyloid accumulating animals compared with healthy littermate control. Future experiments will be performed in human post-mortem tissue to translate these results from mouse model to the human population. Electrophysiological recordings from acute mouse brain slices were conducted as a functional assay. RESULTS/ANTICIPATED RESULTS: Preliminary results indicate that PNNs are disrupted and that activity-associated levels of PV are reduced. Both inhibitory PV and excitatory pyramidal cell populations exhibit altered spiking and synaptic activity during sharp wave ripple events. DISCUSSION/SIGNIFICANCE OF IMPACT: By elucidating the specific neuronal sub-type that is responsible for hippocampal network disruption, future studies could attempt a targeted optogenetic or pharmacological intervention to restore network activity important for memory consolidation.

2338

Identifying the genetic determinants of human brown adipose tissue

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OBJECTIVES/SPECIFIC AIMS: Brown adipose tissue (BAT) increases energy expenditure by dissipating chemical energy as heat. The combustion of glucose and lipids produces beneficial metabolic effects and renders BAT an attractive target to battle obesity and associated diseases. The majority of adults do not display active BAT on positron emission tomography (PET) without prior cold exposure. Interestingly, a fraction of individuals with BAT positive PET scans exhibits excessive BAT (eBAT) activity, indicating a possible underlying genetic contributor. We aim to identify genetic determinants of BAT activity by studying individuals with eBAT activity using next-generation sequencing. A cellular model will be used to validate variants and perform in-depth pathway analysis. METHODS/STUDY POPULATION: We performed a retrospective review of PET scans over a period of 12 months in patients presenting with suspected or diagnosed cancer (n = 20,348). The distribution of BAT positive individuals (n = 1251) was used to implement a threshold to define eBAT activity. Samples from prospectively recruited individuals with BAT activity above the threshold will undergo whole exome sequencing. Variants associated with eBAT activity will be engineered into an immortalized BAT cell line using CRISPR to validate results and perform in-depth pathway analysis. RESULTS/ANTICIPATED RESULTS: We expect to identify genetic variants associated with eBAT. Studying the effects of these variants on thermogenesis followed by in-depth pathway analysis in genetically engineered cellular and mouse models may enable us to find new regulators of BAT activity. These findings may eventually contribute to the development of new drugs targeting obesity and its sequelae. DISCUSSION/SIGNIFICANCE OF IMPACT: The contribution of genetic factors to individual BAT activity is currently unknown. Identifying individuals with eBAT on PET scans and studying the underlying genetic determinants may provide the foundation for the discovery of new pathways for BAT activation.

2050

Identifying the role and immunobiological mechanisms of Fli-1 mediated pathogenicity in graft Versus host disease

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OBJECTIVES/SPECIFIC AIMS: Allogeneic hematopoietic stem cell transplantation (allo-HCT) is a curative procedure for hematological malignancies. Chronic graft Versus host disease (cGVHD) is a lethal complication that often develops after allo-HCT. Fli-1 is an aberrantly expressed protein in cancers including erythroleukemia and melanoma, while being implicated in pathogenesis of systemic lupus in mice and humans, a disease with marked similarity to cGVHD. METHODS/STUDY POPULATION: cGVHD was induced using hematopoietic cells from conditional knock-out mice deficient for the fli-1 gene specifically on T cells and progression of cGVHD in murine allo-HCT recipients was

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monitored using a clinical scoring system, and changes in activation status of hematopoietic cell populations were quantified using flow cytometry. RESULTS/ANTICIPATED RESULTS: Recipients transplanted with fli-1 deficient T cells exhibited reduced cGVHD clinical scores compared with littermate wild-type controls. Donor-grafts containing fli-1 deficient T cells were associated with restrained T-cell responses including reduced Interferon-γ cytokine production, PD-1 expression, and differentiation into follicular helper T cells. fli-1 T-cell deficient donor-grafts also improved donor B-cell reconstitution and reduced plasma cells in allo-HCT recipients relative to littermate wild-type control donor-graft recipients. DISCUSSION/SIGNIFICANCE OF IMPACT: Thus, inhibiting Fli-1 represents a promising therapeutic strategy for the goal of preventing cGVHD after allo-HCT while also directly targeting cancers which aberrantly express Fli-1.

2333

Impact of spoken sentence predictability on cognitive spare capacity in elderly adults with hearing loss

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OBJECTIVES/SPECIFIC AIMS: Listening effort is needed to understand speech that is degraded by hearing loss and/or a noisy environment. Effortful listening reduces cognitive spare capacity (CSC). Predictive contexts aid speech perception accuracy, but it is not known whether the use of context reduces or preserves CSC. Here, we compare the impact of predictive context and cognitive load on behavioral indices of CSC in elderly, hearing-impaired adults. METHODS/STUDY POPULATION: Elderly, hearing-impaired adults listened in a noisy background to spoken sentences in which sentence-final words were either predictable or not predictable based on the sentence context. Cognitive load was manipulated by asking participants to remember either short or long sequences of visually presented digits. Participants were divided into low or high cognitive capacity groups based on a pretest of working memory. Accuracy and response times were examined for report of both sentence-final words and digit sequences. RESULTS/ANTICIPATED RESULTS: Preliminary results indicate that accuracy and response times for both words and digits were facilitated by sentence predictability, suggesting that the use of predictive sentence context preserves CSC. Response times for both words and digits and accuracy for digits were impaired under cognitive load. Trends were similar across high and low cognitive capacity groups. The preliminary results support the idea that habilitation strategies involving context use could potentially support CSC in elderly, hearing-impaired adults. DISCUSSION/SIGNIFICANCE OF IMPACT: These preliminary results support the concept that habilitation strategies involving context use could potentially support CSC in elderly, hearing-impaired adults.

2302

Impacts of postnatal nest change on early development

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OBJECTIVES/SPECIFIC AIMS: It has been reported that birth mode affects development, with cesarean section born mice gaining more body weight during development. Since mice C-sections involve fostering and nest change, we sought to determine whether changing only the nest and cage would have an effect on development. METHODS/STUDY POPULATION: A total of 53 mice were born to 9 dams, and 21 babies (4 litters) were exchanged in pairs to foreign cages and nests. Litters were followed for body weight and mothers were observed during periods for maternal and nonmaternal behaviors. RESULTS/ANTICIPATED RESULTS: The results show that average body weight was significantly higher in the experimental group in both genders, with 20% higher body weights at weaning. The mothers from the litters that were changed to a new nest showed significantly more non-maternal behavior in the first 2 days if life, than the controls. DISCUSSION/SIGNIFICANCE OF IMPACT: The results suggest that changes in maternal behavior may be linked to the increased weight gain in their babies.

2461

Increasing butyrate levels by microbial manipulation or drug administration to delay Parkinson's disease progression

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OBJECTIVES/SPECIFIC AIMS: Determine if synthetic or endogenously produced butyrate can delay Parkinson's disease (PD) progression, attenuate PD associated GI dysfunction, and impact the gut-microbiota in mice expressing human mutant aSyn. METHODS/STUDY POPULATION: Two transgenic mouse models expressing human mutant alpha-synuclein (aSyn) will be used. Transgenic mice expressing aSyn A53T display GI dysfunction before motor deficit onset and will be used to investigate treatment impact on PD associated GI dysfunction. Mice expressing aSyn Y39C more accurately recapitulate age-related neuropathology and behavioral deficits and will be used to assess treatment impact on PD-associated neuropathology, motor, and cognitive function. Mice will receive a synthetic sodium butyrate, sodium phenylbutyrate, or a synbiotic treatment regimen for 3 months. Disease progression will be assessed by aSyn brain and gut neuropathology, brain and gut inflammatory status, behavioral deficits, and gastrointestinal function. In addition, fecal and gut-microbiota composition and neuroprotective gene expression in the brain will be investigated. RESULTS/ANTICIPATED RESULTS: Our preliminary data shows that both sodium butyrate and sodium phenylbutyrate delay disease progression in aSyn Y39C mice. Butyrate-treated mice have reduced aSyn oligomerization, reduced Lewy body formation, and improved motor and cognitive function compared to placebo-treated mice. 16S rRNA sequencing did not reveal fecal-microbiota shifts between treatment groups or with age progression. Further analysis assessing expression levels for genes with anti-oxidant and protein degradation roles will be performed to determine if sodium butyrate and sodium phenylbutyrate similarly impact cellular mechanisms to delay neurodegeneration. Our future experiments will focus on comparing sodium butyrate and synbiotic treatment outcomes in aSyn A53T mice. DISCUSSION/SIGNIFICANCE OF IMPACT: Our lab developed a Tg mouse model that more accurately recapitulate age-related symptoms, pathology, and mechanisms observed in PD patients compared with animal models onset by neurotoxins. Our use of an age-dependent model of a severe form of Parkinsonism, DLB, will better predict clinical outcomes in PD populations. We will be the first to assess if elevating select microbial product production enhances neuroprotective brain activity in a PD model. Results obtained will further characterize gut-brain axis communication mechanisms. These proposed experiments will be the first to determine if elevating microbial products improves GI deficits associated with PD and may lead to insight on the gut-brain axis role in PD. Overall, this proposal will be the first to investigate a novel, highly accessible treatment with the potential to delay PD progression and target motor, cognitive, and GI deficits associated with PD. Due to the current FDA approval of probiotics and prebiotics that enhance butyrate production, results obtained may be quickly translated for clinical use.

2363

Inducing anti-tumor immunity in colorectal cancer

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OBJECTIVES/SPECIFIC AIMS: Despite significant advances in screening and treatment, colorectal cancer is the second leading cancer killer in the United States today. Some of the most promising recent developments in cancer therapy have come from immune-based therapy. Immune-based therapy, however, has shown limited utility in patients with colorectal cancer. Studies have previously shown that certain chemotherapy regimens may be more effective in combination with immune-based therapy due to induction of inflammation in the tumor microenvironment. In this study, we sought to determine how standard chemotherapy (FOLFOX) affects the generation of antigen-specific anti-tumor immunity in colorectal cancer. METHODS/STUDY POPULATION: To determine the how antigen-specific immunity and T cell

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