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 Fl^{-} deficient T cells were associated with restrained T-cell responses including reduced Interferon-Y cytokine production, PD-I expression, and differentiation into follicular helper T cells. Fl^{-} T-cell deficient donor-grafts also improved donor B-cell reconstitution and reduced plasma cell relative to littermate wild-type control donor-graft recipients. DISCUSSION/SIGNIFICANCE OF IMPACT: Thus, inhibiting Fl^{-} represents a promising therapeutic strategy for the goal of preventing cGVHD after allo-HCT while also directly targeting cancers which aberrantly express Fl^{-}.

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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.

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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 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 control litters. DISCUSSION/SIGNIFICANCE OF IMPACT: The results suggest that changes in maternal behavior may be linked to the increased weight gain in their babies.

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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 α-syn. METHODS/STUDY POPULATION: Two transgenic mouse models expressing human mutant alpha-synuclein (α-syn) will be used. Transgenic mice expressing α-syn A53T display GI dysfunction before motor deficit onset and will be used to investigate treatment impact on PD associated GI dysfunction. Mice expressing α-syn 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. Mouse will receive a synthetic sodium butyrate, sodium phenylbutyrate, or a symbiotic treatment regimen for 3 months. Disease progression will be assessed by α-syn 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 α-syn Y39C mice. Butyrate-treated mice have reduced α-syn 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 of genes 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 symbiotic treatment outcomes in α-syn 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 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.

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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) levels affects the generation of antigen-specific anti-tumor immunity in colorectal cancer. METHODS/STUDY POPULATION: To determine how the antigen-specific immunity and T cell
responses are affected by FOLFOX, we utilized a model antigen expressing murine colon cancer cell line syngeneic to C57BL/6 (MC38-CEA). Treatment was performed when tumors reached 50 mm diameter. Tumor-bearing mice were treated with FOLFOX vehicle (PBS), 5-Fluorouracil (5-FU), Oxaliplatin, or combination (FOLFOX). Antigen-specific cytotoxic T cell (tet + Tc) were detected using Db-CEATetramer obtained from the NIH-tetramer core facility. Flow cytometry was performed for phenotypic analysis and tetramer positivity. Tumor growth was measured using standard caliper measurements. Statistical analysis was performed using t-test for continuous variables and ANOVA was used when comparing multiple groups. Statistical analysis was performed using SPSS. All arms were completed with n = 3–7. RESULTS/ANTICIPATED RESULTS: To determine how systemic treatment with chemotherapy affects cytotoxic T cell development (Tc), we established that we could detect antigen-specific Tc (tet + Tc) in the spleen, tumor, and draining lymph nodes of tumor-bearing mice. After establishing that the system worked appropriately, tumor-bearing mice were treated with different chemotherapy regimens and tumor growth was monitored. As expected, the combination of FOLFOX was significantly better than either drug individually (2-way ANOVA, p < 0.01). FOLFOX therapy also showed a significant (p < 0.05) increase in the number of tumor-associated antigen-specific tet + Tc expressing phenotypic markers of effector (Te) and resident memory (Trm) subsets. Tumor-associated tet + Tc highly expressed PD-1 (>50%); however, this was not significantly different between treatment or vehicle arms. Since 5-FU, one component of FOLFOX has previously shown a selective reduction of myeloid-derived suppressor cells, we also investigated the myeloid compartment. There were no significant differences in conventional or plasmacytoid dendritic cells, myeloid-derived suppressor cells, or tumor-associated macrophages.

DISCUSSION/SIGNIFICANCE OF IMPACT: The future of cancer care involves multi-modality care sup- pressor cells, or tumor-associated macrophages. DISCUSSION/SIGNIFICANCE OF IMPACT: The future of cancer care involves multi-modality care to tailor treatments. To more effectively combine therapy it is critical that we understand how currently utilized therapy works. In this study, we show that the primary chemotherapy regimen utilized in colorectal cancer increases tumor-associated antigen-specific tet + Tc cells throughout the life of an individual. METHODS/STUDY POPULATION: ASCs and bmMSCs were isolated from patient donors. The following samples were collected: ASCs from 3 young (under the age of 59) and lean (BMI < 30) patients, ASCs from 3 older patients (over the age of 59), ASCs from 3 patients with BMI > 30, and bmMSCs from 4 young and lean patients. Cytoplasmic RNA from the cell populations was isolated and sequenced by RNA-Seq from the cell populations. Using our recently developed bioinformatics pipeline, we set out to quantify L1 expression and identify the few ‘sufficient L1s at specific loci that are actively transcribing to RNA in the ASC and bMSC samples. RESULTS/ANTICIPATED RESULTS: Here we provide proof of concept with the application of this novel method in characterizing full-length expressed L1s at the specific loci level in ASCs and bMSCs. We identified L1 loci that are commonly expressed in these cell types and observed an increase in L1 expression in the obese and old ASC cells compared with the young, lean ASCs and bMSCs. DISCUSSION/SIGNIFICANCE OF IMPACT: ASCs show the promise of broad application in the biomedical field including regenerative treatment. There are reports that ASCs cultivated from older and obese donors are less effective for regenerative treatments. By demonstrating an increased expression of the mutagenic L1 element in ASCs from obese and old donors, this study provides further evidence suggesting the preferable use of ASCs from young and lean donors for regenerative therapies. These studies will also help us to understand the potential contribution of L1 expression to loss of stem cell function during the aging process.

Lafora disease premature termination codons (PTCs) are likely candidates for suppression by aminoglycosides

To determine whether patients with a genetic disease, a nonsense/STOP mutation/premature termination codon (PTC) is the underlying cause of their malady, PTCs prematurely stop protein synthesis and yield truncated proteins. Truncated proteins potentially provide little to no proper function or activity and are rapidly degraded; thus, disease is imminent. Recent work has demonstrated that small molecules including aminoglycosides can cause the ribosome to readthrough these PTCs. Thus, PTC readthrough with small molecules is a very attractive approach for treating diseases caused by PTCs. Small molecules that promote readthrough act on the ribosome and induce a ribosomal conformational change. In this conformation, the PTC is not recognized by the translational machinery and an amino acid is incorporated into the growing peptide chain, thus protein synthesis continues without a stop. The use of a single small molecule to readthrough various PTC mutations has been repeatedly effective for in vitro studies and some of these have progressed to clinical trials. Although there has been success in defining these small molecules, the field has discovered that every PTC is unique and likely requires a different small molecule. Thus, developing a cell culture model to test read-through of Lafora PTCs and the functionality of the protein product is the first step to developing a readthrough therapy for a LD. METHODS/STUDY POPULATION: Method for in vitro quantification of