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Coffee Shops and Fast-food Restaurants: Potential Neighborhood Resources for Cognitive Health and Wellbeing Among Aging Americans

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OBJECTIVES/GOALS: Environmental factors may significantly increase the risk of or buffer against Alzheimer's disease and related dementias, yet strategies to address cognitive decline and impairment to date largely overlook the role of neighborhoods. This mixed-methods study is the first to examine potential links between access to eateries and cognitive function. The goal is to inform place-specific interventions to help aging individuals reduce risk for cognitive impairment through neighborhood community and design. METHODS/STUDY POPULATION: Following an exploratory sequential mixed-methods design, seated and mobile interviews with 125 adults aged 55-92 (mean age 71) living in the Minneapolis (Minnesota) metropolitan area suggest that eateries, including coffee shops and fast-food restaurants, represent popular neighborhood destinations for older adults and sources of wellbeing. To test the hypothesis that these sites, and the benefits they confer, are associated with cognitive welfare, we analyzed data from urban and suburban dwelling participants in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a national racially diverse sample of older Americans followed since 2003 (n = 16,404, average age at assessment 72 years). RESULTS/ANTICIPATED RESULTS: Qualitative thematic analysis of how older adults perceived and utilized local eateries include sites of familiarity and comfort; physical and economic accessibility; sociability with friends, family, staff, and customers; and entertainment (e.g., destinations for outings and walks, free newspapers to read). Quantitative results from multilevel linear regression models demonstrate a positive association between density of eateries and cognitive functioning. Taken together, these results complicate our understanding of fast-food settings as possible sites of wellbeing through social interaction and leisure activities. DISCUSSION/SIGNIFICANCE OF IMPACT: The results contribute new evidence towards an emerging ecological model of cognitive health. Understanding whether and how retail food environments can help buffer against cognitive decline among older adults provides novel opportunities to promote wellbeing in later life through community interventions and neighborhood design.

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Collagen Dermal Replacement Scaffold Mechanobiology in Treatment of Difficult-to-Heal Wounds

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OBJECTIVES/GOALS: Difficult-to-heal wounds of the skin are a common and costly medical problem. Dermal replacement strategies have emerged as a solution, but a challenge is identification of optimal scaffold parameters. We present a model for assessment of clinical potential of collagen scaffolds for wound healing. METHODS/STUDY POPULATION: In previous animal experiments, we evaluated dermal replacement scaffolds custom-fabricated from fibril-forming collagen oligomer with controlled fibril density (4, 20, 40mg/cm^3) and spatial gradients in rat excisional wounds. Wound contraction and cellularization were monitored by gross and histological image analysis for comparison with model outcomes. We now parameterize the scaffold parameters for use in the mathematical model of wound healing with nonlinear curve fitting. A preliminary chemo-bio-mechanical finite element model including collagen, cells, and an inflammatory signal was adapted to simulate wound healing results. RESULTS/ANTICIPATED RESULTS: Collagen oligomer microstructure was quantified from scanning electron micrographs. A constitutive law for collagen mechanics was fit to experimental uniaxial tensile tests. We have conducted preliminary three-dimensional finite element model simulations to be validated against experimental wound contraction, recellularization, and collagen remodeling data collected from each experimental group. We show the effects of collagen density and stiffness on wound contraction by altering early wound mechanical properties. We anticipate future work to further improve the model of mechanotransduction, inflammation, and recellularization. DISCUSSION/SIGNIFICANCE OF IMPACT: This work represents the first step towards a computational model of wounds treated with collagen scaffold dermal replacements. In turn, the model will be used to explore cell-scaffold interactions for purposes of prediction and optimization of tissue regeneration outcomes.

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DEEP-PRIMED IL-15 SUPERAGONIST IMPROVES ANTIVIRAL EFFICACY OF HIV-SPECIFIC CD8$^+$ T-CELLS IN HUMANIZED MOUSE MODEL

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OBJECTIVES/GOALS: HIV-specific CD8$^+$ T-cells play a critical role in partially controlling viral replication in infected-individuals, but ultimately fail to eliminate infection. Enhancing these T-cell responses through lymphocyte engineering approaches has the potential as a novel therapy capable of achieving durable control or eradication of infection. METHODS/STUDY POPULATION: IL-15 Superagonist (IL-15SA) potently supports the *in vivo* persistence and antiviral activity of adoptively transferred CD8$^+$ T-cells. The Deep-Priming^{TM} technology platform, developed by Torque, allows for loading of immunomodulators onto the surface of T-cells via electrostatic 'nanogels', which slowly release to deliver sustained autocrine immune stimulation without the harmful effects of systemic exposure. Here, we investigate the impact of IL-15SA Deep-Priming on HIV-specific CD8$^+$ T-cells in a humanized mouse model of HIV infection. Humanized mice were generated by engrafting NOD-*scid*-IL2Rg^{null} mice with memory CD4$^+$ T-cells isolated from an ARV-suppressed HIV+ donor. An autologous HIV-specific Cytotoxic T-Lymphocyte (CTL) clone was isolated, and killing potential confirmed. Four weeks post humanization, mice were infected with HIV and received an infusion of unmodified HIV-Specific CTLs, or IL-15SA Deep-Primed HIV-specific CTLs (CTL-DP). T-cell numbers and plasma viral loads were quantified weekly by flow cytometry and qRT-PCR. RESULTS/ANTICIPATED RESULTS: Mice receiving unmodified CTLs trended toward reduced viral loads compared to the No Treatment condition, while mice receiving CTL-DP saw significant, 2-Log$_{10}$ reductions in VL ($p<0.01$). At 41 days post-infection 100% (5/5) of the No Treatment, 66.7% (4/6) of the CTL treatment, and 16.7% (1/6) of CTL-DP treatment mice had

https://doi.org/10.1017/cts.2020.59 Published online by Cambridge University Press

detectable viremia. IL-15SA Deep-Priming increased CTL expansion and persistence in peripheral blood which correlated with improved $CD4^{+}$T-cell preservation. DISCUSSION/SIGNIFICANCE OF IMPACT: Here we demonstrate the first *in vivo* analysis of IL-15SA Deep-Priming of HIV-Specific CTLs. These data suggest that Deep-Priming of patient T-cells can enhance *in vivo* function and persistence, leading to improved viral suppression; a significant advancement in the field of HIV cure research. CONFLICT OF INTEREST DESCRIPTION: Austin Boesch, Thomas Andresen, and Douglas Jones are employees of Torque. Darrell Irvine is a co-founder of Torque and Chairman of Torque's Scientific Advisory Board.

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Defining the role of non-canonical PIK3CA mutations in head and neck squamous cell carcinoma

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OBJECTIVES/GOALS: To characterize the oncogenic potential of HNSCC cell lines harboring 17 non-canonical *PIK3CA* mutations. METHODS/STUDY POPULATION: Non-canonical *PIK3CA* mutant constructs generated via site-directed mutagenesis are subcloned into doxycycline-inducible vector pLVX-Puro. Serum-dependent HNSCC cell line (PCI-52-SD1) is then stably transfected with vectors and undergo doxycycline-induction. Cell survival is determined by depriving cells of fetal bovine serum for 72 hours and quantifying remaining cells with 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. Cell proliferation and migration is evaluated with colony formation assays and transwell assays respectively. RESULTS/ANTICIPATED RESULTS: To date, the survival behavior of eight non-canonical mutants was assessed. Three mutants – Q75E, V71I, and E970K – exhibited 18.7-26.7% greater survival rate relative to cells transfected with wild-type. Five mutants – R519G, Y606C, W328S, C905S, and M1040I – demonstrated survival rates that differed only by −4.3% to +6.6% relative to wild-type. We hypothesize the three activating mutants that exhibited increased survival will also demonstrate increased cell proliferation and migratory behavior whereas the three neutral mutants will not differ from control. DISCUSSION/SIGNIFICANCE OF IMPACT: Ongoing HNSCC PI3K inhibitor trials could be more effective if all *PIK3CA* hyperactivation mutations are known. Identifying non-canonical mutation effects could result in greater efficacy if drugs are restricted only to those with activating mutations. CONFLICT OF INTEREST DESCRIPTION: JRG and DEJ are co-inventors of cyclic STAT3 decoy and have financial interests in STAT3 Therapeutics, Inc. STAT3 Therapeutics, Inc. holds an interest in a cyclic STAT3 decoy oligonucleotide. The remaining authors declare no conflicts.

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Development of a Mouse Model to study interactions between parental history of alcohol use and early life adversity on behavioral and neurobiological development of offspring

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OBJECTIVES/GOALS: Individuals with a family history of alcoholism (FH+) are more likely to develop an alcohol use disorder than those with no such history. Early life adversity has a high coincidence with FH+ making pathogenic studies difficult in clinical studies. Here, we developed a mouse model to study pathogenic mechanisms underlying these risk factors. METHODS/STUDY POPULATION: Male and female C57BL6/J mice were exposed to increasing concentrations of ethanol (3-21%) or water for 15 days prior to breeding. Ethanol was not present during gestation. Offspring were either removed from the home cage and isolated for 3 hours or left undisturbed from postnatal days 1-21. Beginning on PND 56 offspring mice were assessed for clinically relevant behavioral disruptions in social behavior, cognitive working memory, locomotor activity, anxiety-like phenotypes, ethanol preference and binge drinking behavior. In a separate experiment, brains of $Cx3cr2^{+/GFP}xCcr2^{+/RFP}$ mice from ELA or control conditions were collected every 7 days after birth for assessment of neuroinflammation and central immune cell morphology and density. RESULTS/ANTICIPATED RESULTS: Mice with a family history of ethanol exposure and ELA are predicted to exhibit behavioral changes (impaired working memory, reduced social behavior, increased anxiety-like behaviors, increased ethanol consumption) to a greater extent than mice with a family history of ethanol exposure or ELA alone. We expect markers of neuroinflammation (cytokine expression, immune cell activation) to predict the behavioral changes in these mice. DISCUSSION/SIGNIFICANCE OF IMPACT: Alcohol consumption and stressful life events are known environmental precipitants to neuroinflammation, which in turns may predispose individuals to anti-social and risky behavior. A mouse model of these early postnatal conditions will allow basic scientists to unravel the biological underpinnings of the behaviors driven by these factors.

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Dissecting the role of microenvironment heterogeneity on metastatic tumor cell phenotype at an engineered metastatic niche

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OBJECTIVES/GOALS: Breast cancer metastases are stochastic and difficult to detect. Therapy is often ineffective due to phenotypic changes of tumor cells at these sites. We engineered a synthetic metastatic niche to study the role of phenotypic transitions in the microenvironment on tumor cell phenotype. METHODS/STUDY POPULATION: The engineered metastatic niche is composed of a porous polycaprolactone scaffold implanted subcutaneously in Balb/c mice. The mice received an orthotopic inoculation of 4T1 cells (murine triple negative breast cancer) in the fourth right mammary fat pad and the disease was allowed to progress for 7-21 days (pre-metastatic to overt metastatic disease). The scaffolds and lungs (native metastatic site) were explanted and analyzed by single cell RNA-seq via Drop-seq. Cell phenotypes were identified and tracked over time with the Seurat and Monocle3 pipelines. Assessment of the impact of these cell populations on tumor cell phenotype was conducted through Transwell co-cultures. RESULTS/ANTICIPATED RESULTS: Healthy scaffolds are primarily composed of macrophages, dendritic cells, and fibroblasts – consistent with a foreign body response. Despite differences in the lung and scaffold prior to tumor inoculation, both tissues were marked by >5-fold increase in neutrophils/MDSCs. Additionally, 79% of genes at the scaffold that significantly changed over time were also identified in the lung, indicating key similarities in niche maturation. However, many immune cells at the scaffold had distinct phenotypes, with pro-

https://doi.org/10.1017/cts.2020.59 Published online by Cambridge University Press