higher burden among certain demographic groups. Measures are required to arrest this ominous trend and to eliminate the disparities in outcome among patients hospitalized with NAFLD.

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Reconstruction of Patient-specific Distal Airway Regeneration Patterns in COPD

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OBJECTIVES/SPECIFIC AIMS: The objective of this study was to reconstruct patient-specific distal airway patterns at the tissue- and single-cell resolution and develop personalized distal airway models based on utilization of patient-derived DABCs and autologous region-specific stromal cells. METHODS/STUDY POPULATION: Patient-specific distal airway units, containing parental small bronchiole (<2 mm in diameter, >12th generation) and daughter airway branches, including pre-terminal/terminal bronchioles, leading to alveoli (3-7 units/lung), were dissected. Epithelial and stromal cells were isolated from these units and processed for ddSeq single-cell RNA-sequencing (n=6 samples). Autologous DABCs and stromal cells were isolated, propagated, biobanked, and used for establishment of patient-specific distal airway models (3D-organoids and air-liquid interface-based airway wall model; n=10 samples). Region-specific tissue patterns were evaluated using immunofluorescence and laser-capture microdissection (LCM; n=6 samples). RESULTS/ANTICIPATED RESULTS: Single-cell-based human distal airway transcriptome map (constructed based on the analysis of >6,500 distal airway cells obtained from 6 subjects) identified physiological and COPD-relevant distal airway differentiation patterns, including distal airway-specific secretory phenotype (DASP) characterized with high expression of secretoglobins 3A2 and 3A1, surfactant proteins SFTPB and SFTPA2, and mucin 1, unique signatures of DABCs, and stromal (fibroblasts, smooth muscle, endothelial cell subpopulations) and immune (macrophage, T cells, B cell, mast cells). Immunofluorescence analysis and LCM confirmed distribution of cell type-specific markers with differential expression patterns of DABC and DASP signatures. Patient-derived DABC-stromal co-culture models reproduced 3 regenerative patterns: 1) physiological (high DABC-clonogenic potency, establishment of polarized differentiated organoids and DASP-expressing epithelia); 2) hypo-regenerative (failure of DABCs to form clones, spheres and mechanically stable differentiated epithelial barrier); and 3) hyperplastic (generation of DABC hyperplasia accompanied in some COPD samples by mucous-cell hyperplasia mimicking in vivo remodeling patterns). DISCUSSION/SIGNIFICANCE OF IMPACT: Patient-specific maps and models of distal airway regeneration patterns have been established in this study, which can be used to identify candidate pathways that mediate disease-relevant airway remodeling and potentially utilized as pre-clinical platforms for developing personalized therapeutic approaches to suppress the progression of distal airway remodeling in chronic lung diseases, including COPD.

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Relation between Dopamine Transporter (DAT1) polymorphism and subjective effects of alcohol among non-dependent drinkers

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OBJECTIVES/SPECIFIC AIMS: Dopamine transporter (DAT1) gene variation is associated with reward-related phenotypes including alcohol response. There is also evidence for a potential moderating role for mu-opioid receptor (OPRM1) gene variation on the relationship between DAT1 variation and alcohol response measures. We aimed at studying the interaction between the DAT1 VNTR and OPRM1 A118G polymorphisms on alcohol consumption and subjective responses among non-dependent drinkers. METHODS/STUDY POPULATION: We employed a progressive ratio (PR) paradigm of intravenous alcohol self-administration (IV-ASA) using the Computer-Assisted Infusion System (CAIS) to assess the motivation for alcohol seeking and consumption in a sample of nondependent drinkers. We used the Drug Effects Questionnaire (DEQ) and Biphasic Alcohol Effects Questionnaire (BAES) to assess subjective response. IV-ASA measures included average breath alcohol concentration (BrAC) and total ethanol infused. Peripheral blood samples were collected for genotyping. Ethics approval was obtained from the NIH Addictions Institutional Review Board. RESULTS/ANTICIPATED RESULTS: Fifty participants completed the PR IV-ASA session after informed consent. There were significant interactions between the DAT1 and OPRM1 genotypes in subjective effects of alcohol. Simple main effects analysis showed that DAT1 10a allele carriers that were also OPRM1 G allele carriers had significantly higher scores for several measures: "feel the drug effects" ($F(1,46)=6.573$, $P = 0.014$), "feel intoxicated" ($F(1,46)=8.613$, $P = 0.005$) and "feeling high" ($F(1,46)=10.889$, $P = 0.002$) in DEQ and higher sedation ($F(1,46)=4.575$, $P = 0.038$) in BAES. The genotypes statistically significantly predicted average breath alcohol ($F(1,61) =3.295$, $p=0.044$) and total ethanol infused ($F(1,61)=3.632$, $p=0.032$. DAT1 VNTR and OPRM1 A118G polymorphisms taken together accounted for 6.9 and 7.8% of variations in average breath alcohol and total ethanol infused respectively. DISCUSSION/SIGNIFICANCE OF IMPACT: Polymorphic variations in DAT1 and OPRM1 interact with each other in determining subjective effects of alcohol in intravenous alcohol infusion assessing motivation for alcohol seeking and consumption in nondependent drinkers. These epistatic interactions in subjective effects of alcohol are salient in the context of predicting and understanding neurobiological effects of alcohol and thereby the therapeutic responses in treating alcohol use disorders.

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Super Bingers: Traits and Patterns Associated with High-Intensity Drinking

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OBJECTIVES/SPECIFIC AIMS: This study attempts to evaluate the drinking patterns and traits of individuals who partake in high intensity drinking, defined as binge drinking at 2 or more times

https://doi.org/10.1017/cts.2019.354 Published online by Cambridge University Press

the minimum binge count (4 drinks for females, 5 drinks for males). METHODS/STUDY POPULATION: We analyzed data from non-treatment seeking volunteers enrolled in NIAAA screening protocols. The sample included 706 males and 474 females ranging in age from 18 to 91. Subjects were assigned to one of four groups (Non-Binge, Level 1, Level 2, Level 3) based on the highest binge session reported in their Timeline Followback questionnaire. The criteria for each group were different for males and females based on the current NIAAA definitions of binge drinking. The cutoffs for females were 0-3 drinks for Non-Binge, 4-7 drinks for Level 1, 8-11 drinks for Level 2, and 12+ drinks for Level 3. The male drink cutoffs were 0-4, 5-9, 10-14, and 15+ respectively. We looked at various drinking measures (Timeline Followback, Self-Reported Effects of Alcohol (SRE), Alcohol Use Disorders Identification Test (AUDIT)) and trait measures (UPPS-P Impulsivity Scale, Barratt's Impulsiveness Scale, Buss Perry Aggression Questionnaire) to identify mean differences between groups. RESULTS/ANTICIPATED RESULTS: There were significant differences in drinking patterns between the groups for both males and females. Number of drinking days, average drinks per drinking day, and number of heavy drinking days all increased as binge level increased. There were also significant differences between groups in males for trait measures. Level 2 and Level 3 bingers scored significantly higher on impulsivity and aggression than the Level 1 and Non-Binge groups. Ongoing analyses are examining differences among binge groups on other measures including SRE and AUDIT. Future analyses will explore potential mechanisms underlying the relationships between trait measures and binge drinking using structural equation modeling. DISCUSSION/SIGNIFICANCE OF IMPACT: This study found significant differences between high-intensity drinkers, or "super bingers", and lighter binge and non-binge drinkers. Super bingers showed an overall heavier drinking pattern across measures. The elevated aggression, impulsivity, and overall heavy drinking patterns of super bingers suggest a behavioral profile that makes this group in particular at higher risk for developing alcohol use disorder and related problems. These traits and behaviors may also help identify targets for treatment interventions for alcohol use disorder.

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Surgical Adjuvant of Immunomodulatory Gene Circuits for Treatment of Glioblastoma

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OBJECTIVES/SPECIFIC AIMS: Glioblastoma (GBM) is a brain cancer with a devastatingly short overall survival of under two years. The poor prognosis of GBM is largely due to cell invasion and maintenance of cancer initiating cells that evade the brain's innate and adaptive immune responses which enables escape from surgical resection and drives inevitable recurrence. While targeting the brain's immune microenvironment has long been proposed as a strategy for treating GBM, translational progress has been slow, underscoring the need to investigate the brain's immune microenvironment for therapeutic avenues. METHODS/STUDY POPULATION: Recent advancements in tunable synthetic immunomodulatory gene circuits targeting metastatic cancers has demonstrated the novel ability to use engineering principles to induce infiltrative cancer cells to express combinatorial immunomodulatory outputs that enable T-cell killing4. Our central hypothesis is: we will be able to significantly improve survival with a lasting immune-mediated control of GBM by using synthetic immunomodulatory gene circuits driving GBM cells to express a local combination of immunomodulatory proteins: human IL15, a surface T-cell engager, PD-L1-CD3 bispecific antibody, and the protein, LIGHT (TNFRSF14). Importantly, the co-expression of LIGHT and anti-PD-L1 therapies was recently shown to rescue PD-L1 checkpoint blockage in the preclinical models of brain tumors and significant enhance survival outcomes highlighting the benefits of novel combinations of immunomodulatory proteins for treatment of GBM. To identify genes whose expression is dramatically upregulated in GBM compared to normal human brain cells, a pooled of six thousand lentiviral oncogene promoters that drive expression of a red-fluorescent protein has been infected into three human GBM cell lines. RESULTS/ANTICIPATED RESULTS: We have successfully infected our GBM cells and are preparing samples for next generation DNA sequencing to determine highly active promoters in GBM that are not expressed in multiple normal brain cells types, astrocytes and neurons. These chosen promoters will then be used to drive an AND gate logic gene circuit immunotherapy outputs which is currently under development for both in-vitro and in-vivo experiments. DISCUSSION/SIGNIFICANCE OF IMPACT: We anticipate that local expression of multiple immune effectors proteins will significantly enhance tumor control and survival in both synergistic murine and human-murine xenograft pre-clinical models of GBM. Ultimately, our goal is to rapidly translate this technology advance into the clinical trial for adult GBM patients.

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TARGETING DIABETES PREVENTION PROGRAMS: INDIVIDUAL RISK-BASED HEALTH ECONOMIC ANALYSIS

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OBJECTIVES/SPECIFIC AIMS: Objective: Approximately 86 million people in the US have prediabetes, but only a fraction of them receive proven effective therapies to prevent diabetes. Further, the effectiveness of these therapies varies with individual risk of progression to diabetes. We estimated the value of targeting those individuals at highest diabetes risk for treatment, compared to treating all individuals meeting inclusion criteria for the Diabetes Prevention Program (DPP). METHODS/STUDY POPULATION: METHODS: Using a micro-simulation model, we estimated total lifetime costs and quality-adjusted life expectancy (QALE) for individuals receiving: (1) lifestyle intervention involving an intensive program focused on healthy diet and exercise, (2) metformin administration, or (3) no intervention. The model combines several components. First a Cox proportional hazards model predicted onset of diabetes from baseline characteristics for each pre-diabetic individual and yielded a probability distribution for each alternative. We derived this risk model from the Diabetes Prevention Program (DPP) clinical trial data and the follow-up study DPP-OS. The Michigan Diabetes Research Center Model for Diabetes then estimated costs and outcomes for individuals after diabetes diagnosis using standard of care diabetes treatment. Based on individual costs and QALE, we evaluated NMB of the two interventions at population and individual levels,

https://doi.org/10.1017/cts.2019.354 Published online by Cambridge University Press