

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 killing<sup>4</sup>. 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,

stratified by risk quintiles for diabetes onset at 3 years. RESULTS/ANTICIPATED RESULTS: Results: Compared to usual care, lifestyle modification conferred positive benefits for all eligible individuals. Metformin's NMB was negative for the lowest population risk quintile. By avoiding use among individuals who would not benefit, targeted administration of metformin conferred a benefit of \$500-\$800 per person, depending on duration of treatment effect. When treating only 20% of the population (e.g., due to capacity constraints), targeting conferred a NMB of \$14,000-\$18,000 per person for lifestyle modification and \$16,000-\$20,000 for metformin. DISCUSSION/SIGNIFICANCE OF IMPACT: Conclusions: Metformin confers value only among higher risk individuals, so targeting its use is worthwhile. While lifestyle modification confers value for all eligible individuals, prioritizing the intervention to high risk patients when capacity is constrained substantially increases societal benefits.

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### The Role of Suggestibility in Alcohol Use and Misuse

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OBJECTIVES/SPECIFIC AIMS: Suggestibility, defined as the inclination to accept and internalize messages, has not been assessed much in relation to alcohol use. Prior research has shown that suggestibility to social cues and peer influence may play a role in driving alcohol consumption. Our previous work has shown associations between suggestibility and alcohol consumption in social drinkers. This study aims to examine how suggestibility and social susceptibility are related to ideas alcohol consumption and consequences across the spectrum of alcohol use and misuse. We hypothesize that those with higher suggestibility and social susceptibility reports will also have higher alcohol consumption and consequences, and that the impact of susceptibility is lower in dependent compared to non-dependent drinkers. METHODS/STUDY POPULATION: Study participants enrolled in the NIAAA screening and assessment protocol (N=157) completed questionnaires on suggestibility and alcohol consumption, The Multidimensional Iowa Suggestibility Scale (MISS) is a 95-question self-report assessment of suggestibility which draws from subcategories of consumer suggestibility, perceivability, physiological suggestibility, physiological reactivity, and peer conformity. Alcohol measures included 90-day Timeline Followback interviews and the Alcohol Use Disorder Identification Test (AUDIT). Participants also underwent the Structured Clinical Interviews for DSM-IV or DSM-5 disorders, and were stratified into two groups: alcohol dependent (N=86) and non-dependent (N=71). Median split by age was additionally used to explore age's relationship with suggestibility and alcohol with the under 36 (N=45) and over 36 (N=26) non-dependent groups. RESULTS/ANTICIPATED RESULTS: Initial analyses showed marked differences between the dependent and non-dependent groups in the relationship between the MISS total score and AUDIT total score. The non-dependent group showed significant positive correlations between MISS and AUDIT scores ( $r = 0.460$ ,  $p < 0.001$ ), while the dependent group did not show any correlation between MISS and AUDIT scores. Further examination of these relationships in the nondependent group revealed that MISS scores were also significantly positively correlated with AUDIT subscores of consumption, harm, and dependence. Age

was found to have a significant negative correlation with MISS score ( $r = -0.354$ ,  $p < 0.01$ ). To better understand the role of age, the sample was split based on the median age (36 yrs), and analyzed separately. Results indicated robust relationships between MISS score and AUDIT ( $r = 0.457$ ,  $p < 0.01$ ) in the younger age group. In addition, the younger age group also showed significant relationships between MISS score and 90-day TLFB measures of total drinks, days drinking, and heavy drinking days. DISCUSSION/SIGNIFICANCE OF IMPACT: In non-dependent individuals, there was a significant positive relationship between suggestibility and alcohol measures, and these effects were amplified in younger individuals. No relationship was found between suggestibility and alcohol measures in the alcohol dependent individuals. This may be related to a greater impact of social and external contextual cues in younger social drinkers compared to dependent drinkers where tolerance and craving may have greater impact on alcohol consumption. These findings have important implications for traits that may put individuals at risk for developing harmful patterns of alcohol use and misuse. Future analyses will aim to examine biobehavioral underpinnings of the relationship between suggestibility and alcohol consumption.

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### The Study of Fetal Tracheal Occlusion to Treat Congenital Diaphragmatic Hernia in the EXTEND Model

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OBJECTIVES/SPECIFIC AIMS: The goal of this project is to study fetal pulmonary vasculature in a CDH animal model, to understand how FETO affects developing vasculature, and to develop a modifiable fetal tracheal occlusive therapeutic device that avoids previously seen sequelae of FETO, like alveolar distension, decreased surfactant production, and decreased Type II Pneumocytes. The primary outcome is lung volume/kilogram. The secondary outcomes are contrast-enhanced ultrasound perfusion metrics (Time to Peak, Mean Transit Time, Wash-in Rate, Wash-in Perfusion Index), pulmonary vascular density, Lung Injury Histology Scores, and Lung Compliance upon ventilation. METHODS/STUDY POPULATION: Congenital diaphragmatic hernias will be modeled by surgical hernia creation via maternal laparotomy and hysterotomy at gestational age 72 - 74 days. The ewe will undergo a second laparotomy at 105 - 115 days gestational age. After a second hysterotomy is made, the fetus will be removed from the amniotic sac, though placental circulation will be maintained (EXIT Procedure). The animal is cannulated via the umbilical vein and arteries onto the pumpless ECMO circuit. The balloon and pressure sensor complex is placed into the trachea via direct laryngoscopy, and the fetus aseptically sealed into the Biobag. The wires of the tracheal occlusive device (balloon catheter and pressure sensor) will egress via the port of the Biobag. The fetus remains in the Biobag for fourteen days, with the tracheal occlusive device in place for ten days, followed by a four day recovery period. Daily contrast-enhanced ultrasounds and pulmonary artery dopplers are performed. Upon study completion, the fetus is intubated and placed on a conventional ventilator. A full necropsy is then performed, with perfusion fixation of the lungs via the pulmonary artery. RESULTS/ANTICIPATED RESULTS: Hypothesis 1: Modifiable Tracheal Occlusion will have statistically different effects