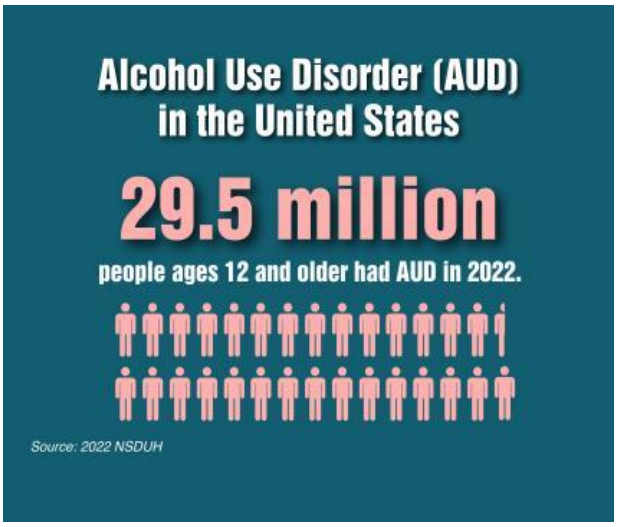
GPR139 AAV Gene Therapy: A Novel Therapeutic Approach to Combat Alcohol Use Disorder

Background



Alcohol Use Disorder (AUD)—previously referred to as alcoholism—a chronic brain disease estimated to affect 14.5 million people in the United States. Based on the 2022 National Survey on Drug Use and Health (NSDUH), 29.5 million people ages 12 and older (10.5% in this age group) had AUD in the past year[1,2]. *According to the Centers for Disease Control and Prevention (CDC), excessive alcohol use leads to over 95,000 deaths in the U.S. every year*[3]. AUD is a prevalent psychiatric condition, characterized by problematic and unhealthy patterns of alcohol consumption. It is a well-recognized disorder that encompasses a broad spectrum of symptoms and behaviors associated with alcohol misuse; however, co-occurrence with drug additions (i.e. opioids) and psychiatric disorders such as schizophrenia, depression, and various personality disorders leads to worsened prognosis. Although the pathogenesis of AUD is not completely understood, multiple factors are believed to contribute to its development – strong scientific evidence supports the influence of specific genes on an individual's susceptibility to developing AUDs. By understanding the molecular mechanisms underlying alcohol dependence, we can identify potential therapeutic targets.

GPR139 AAV Gene Therapy

Pathways Neuro Pharma, Inc. (Pathways) is exploring the critical role of ***G protein-coupled neuroreceptor, GPR139,*** in alcohol dependence, with a specific focus on the medial habenula—a brain region intricately involved in addiction processes. Preclinical studies suggest GPR139 receptor activation can reverse addiction-like behaviors in alcohol-dependent animals, according to a recent study[4]. We are utilizing ***AAV6.2FF*** as a gene delivery platform. AAV6.2FF, an engineered adeno-associated virus (AAV) vector, excels in efficiently delivering genetic material to the cell nucleus. Its unique properties make it an ideal candidate for transporting genes – it has undergone rigorous preclinical safety assessments and does not trigger adverse effects or immune responses, making it a safe choice for clinical applications.

Preliminary data

Gene therapy involves the introduction of a gene - in our application a gene encoding for the production of GPR139 is introduced into the patient with the goal of causing the patient's body to manufacture more GPR139. This additional GPR139 will be localized in the cells where GPR139 naturally resides and functions, namely the habenular cells of the central nervous system. We believe that the habenular cells, fortified with this additional GPR139, will be extra responsive to activation by a pharmaceutical agonist (activator) of GPR139.

Kononoff et al.[4] explored the effects of activating GPR139 using the compound JNJ-63533054. Encouragingly, this activation demonstrated promise in several key areas:

1. Reversing Alcohol Self-Administration Escalation: GPR139 activation led to a reduction in alcohol self-administration escalation. This finding suggests that targeting GPR139 could help curb excessive alcohol consumption.
2. Reducing Withdrawal-Induced Hyperalgesia: Alcohol withdrawal often results in heightened pain sensitivity (hyperalgesia). Activation of GPR139 mitigated this hyperalgesic response, potentially offering relief to individuals experiencing alcohol withdrawal symptoms.

Site-Specific Microinjection: A Novel Approach

Site-specific microinjections were used to further investigate GPR139's potential[4]. These localized injections resulted in even greater reductions in alcohol self-administration and withdrawal-induced hyperalgesia. The data strongly support GPR139 as a novel and promising target for treating alcohol use disorder.

Product development

Pathways gene therapy is a way to provide temporary, but long-lasting therapeutic effect by introducing a new gene into a cell by means of a viral vector. We believe that evidence shows that our vector delivers a stronger response which gives Pathways a competitive advantage. Our preclinical findings from GPR139 receptor studies and AAV6.2FF gene therapy offer exciting possibilities for addressing addiction-related behaviors and disorders. Further research and clinical exploration are crucial to fully realizing the potential of these advancements in the biotechnological landscape.

About the team

Pathways Neuro Pharma, Inc. is developing the first pharmaceutical treatments that target the pathways in the brain that regulate and control the root causes of alcoholism, substance abuse,

depression and associated neurological conditions. Pathways is led by Bradley Thompson, Chief Technology Officer (CTO), with over 39 years experience in autoimmune disease, oncology, and infectious disease, and Anthony Mack, Chief Executive Officer (CEO), with 35-years experience in the pharmaceutical and biotech industries as a C-level executive overseeing the successful development and licensure of several innovative drugs in pain and addiction.

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References:

1. SAMHSA, Center for Behavioral Health Statistics and Quality. 2022 National Survey on Drug Use and Health. Table 5.9A—Alcohol use disorder in past year: among people aged 12 or older; by age group and demographic characteristics, numbers in thousands, 2021 and 2022.
2. SAMHSA, Center for Behavioral Health Statistics and Quality. 2022 National Survey on Drug Use and Health. Table 5.9B—Alcohol use disorder in past year: among people aged 12 or older; by age group and demographic characteristics, percentages, 2021 and 2022.
3. https://www.cdc.gov/alcohol/features/excessive-alcohol-deaths.html
4. Kononoff J, Kallupi M, Kimbrough A, Conlisk D, de Guglielmo G, George O. Systemic and Intra-Habenular Activation of the Orphan G Protein-Coupled Receptor GPR139 Decreases Compulsive-Like Alcohol Drinking and Hyperalgesia in Alcohol-Dependent Rats. eNeuro. 2018 Jul 2;5(3):ENEURO.0153-18.2018. doi: 10.1523/ENEURO.0153-18.2018. PMID: 29971251; PMCID: PMC6027959.

Patents:

Neuroreceptor Compositions and Methods of Use, US Patent Number: 11760788