Research Proposal for the Stanford iGEM Bioengineering Research Program 2024

Use of Artificial Intelligence in Optogenetics and CRISPR-Cas9 Delivery Systems in Treating Chronic and / or Treatment-Resistant Anxiety Disorders

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I. Introduction & Background

Anxiety disorders are among the most prevalent mental health conditions in the world. According to the World Health Organisation, in 2019, 301 million people globally were affected by anxiety disorders[1]. In the United States alone, 19.1% of adults (over 40 million) suffer from an anxiety disorder[2]. Current treatment options include a combination of psychotherapy, like Cognitive Behavioral Therapy, Exposure Therapy, with pharmacotherapy, such as Antidepressants, Benzodiapezines (not recommended for long-term use), Beta – Blockers[3]. Only 1 in 4 affected individuals receives any form of treatment and despite the availability of a wide variety of therapeutic options and combinations, around 30–60% of patients have insufficient response[4]. This leads to chronic and treatment-resistant conditions that impair daily functioning and reduce quality of life, highlighting the critical need for novel approaches tailored to each patient's needs and symptoms presented.

Innovative biotechnologies such as Optogenetics and CRISPR-Cas9, a gene-editing tool (short for "Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9"), present promising new and targeted treatment solutions. Optogenetics is the combination of genetic and optical methods to achieve gain or loss of function of well-defined events in specific cells[5]. For this proposal optogenetics will be used to control neurons that have been genetically modified to express light-sensitive ion channels. This technique allows for precise temporal control over neuronal activity, making it possible to determine which cells and connections across the brain are important in defining and assembling the different features of anxiety**,** while also targeting specific brain regions implicated in anxiety such as the amygdala and prefrontal cortex. CRISPR-Cas9 allows for precise DNA sequence modifications, offering potential corrections to genetic abnormalities associated with anxiety disorders[6].

However, the success of these technologies is heavily dependent on the precision of their delivery systems. The integration of different kinds of Artificial Intelligence (AI) models in these fields can substantially enhance the efficacy of these systems by optimizing targeting accuracy, minimizing off-target effects, predicting patient-specific responses, and providing highly precise interventions, as well as personalized therapy plans Particularly, Machine Learning (ML) and Deep Learning (DL), have revolutionized numerous fields by enabling the analysis of complex datasets and the development of predictive models. AI can also be utilized to identify biomarkers and predict treatment responses.

Objectives

- To explore the use of AI in Optogenetics and CRISPR-Cas9 delivery systems to develop novel treatments for chronic and treatment-resistant anxiety disorders, improve therapeutic outcomes, and lay the groundwork for future neuropsychiatric applications.

- To develop AI algorithms to analyze neural activity data obtained from optogenetic experiments.

II. Research Questions & Hypotheses

Research Questions:

- Can AI improve the precision, efficiency, and safety of viral vector-based delivery systems with Optogenetics and CRISPR-Cas9 gene-editing in treating anxiety disorders? And if so, what are the potential benefits compared to traditional therapies?

- What are the benefits and limitations of integrating AI-driven analysis of genetic and clinical data in terms of tailored treatment outcomes for chronic anxiety disorders?

- How can AI-driven approaches optimize the parameters of optogenetic stimulation and CRISPR-Cas9 gene editing to achieve better therapeutic outcomes?

Hypothesis:

- AI algorithms can improve the targeting accuracy of optogenetic stimulation and neuronal circuits, leading to more effective and personalized treatments for chronic anxiety disorders.

III. Research Design

Research Approach

To carry out this research we will utilize a quantitative research approach ensuring the use of both experimental and computational methods to guarantee robust data collection and analysis.

Sampling Techniques & Data Collection Procedures

To carry out this research we will conduct both in vitro and in vivo experiments complemented by comprehensive data analysis. In detail, we will first validate AI-optimized delivery systems using neuronal cell cultures to assess the precision of targeting and gene editing efficiency. This involves analyzing genomic and transcriptomic data to identify candidate genes involved in anxiety disorders and predicting target sites for gene editing. The efficiency and specificity of gene editing will be evaluated using genomic sequencing technologies and off-target analysis. Additionally, we will use optogenetic stimulation to manipulate neuronal activity and record the activity with fiber optics and electrophysiological techniques. (in vitro validation). Next, we will genetically modify animal models (e.g., mice) to express light-sensitive ion channels in specific brain regions implicated in anxiety.

Concurrently, we will induce anxiety-like behaviors and symptoms in these animals. AI will assist to determine optimal light stimulation parameters to effectively modulate neuronal activity. We will conduct studies to evaluate efficacy and safety of the interventions, monitor behavioral and physiological responses, and assess potential off-target effects (in vivo studies). Behavioral assays (e.g., elevated plus maze, open field test) electrophysiological recordings, and neuronal activity patterns will be used to assess anxiety levels before and after treatment. AI algorithms (trained on data from previous studies to predict the best vector designs) will be used to help design and optimize viral vector systems that can efficiently deliver optogenetic tools and CRISPR-Cas9 components to target brain regions and will be evaluated once again in animal models (in vivo testing). AI algorithms will optimize viral vector selection, dosage, and delivery routes to enhance precision and minimize adverse effects. The performance of these vectors will be assessed through quantitative PCR and fluorescence imaging. Machine learning models will be developed to predict treatment outcomes based on genetic, electrophysiological, and behavioral data. These models will help identify patterns and correlations that might not be evident through traditional analysis methods. Finally, if the preclinical studies demonstrate positive outcomes and validate safety and efficacy, we may proceed to early-phase clinical trials to test AI-optimized delivery systems in human subjects.

AI Models that will be Developed and Used:

1. AI algorithms capable of analyzing large datasets to identify optimal delivery pathways for optogenetics and CRISPR-Cas9.

2. DL: Convolutional Neural Networks for image analysis and identifying precise neuronal targets. Recurrent Neural Networks and Long Short-Term Memory (LSTM) Networks for analyzing time-series data from neuronal activity recordings.

3. Reinforcement Learning (RL): Models to optimize the delivery of optogenetic and CRISPR-Cas9 systems, adjusting parameters based on feedback from in vitro and in vivo experiments.

4. ML: Identify biomarkers associated with anxiety behaviors.

5. Predictive Analytics: Utilize supervised learning models to predict patient-specific responses and optimize personalized treatment plans.

Most of these AI models will be trained with existing datasets on neuronal circuits involved in anxiety disorders and the genetic basis of these conditions.

IV. Safety Review

The experiments designed for this proposal involve the use of potentially hazardous biological reagents, specifically viral vectors and CRISPR-Cas9 components. As such, comprehensive safety measures should be outlined to ensure the well-being of all research personnel, the environment, and the broader community. Key safety measures include:

- Mandatory safety training for all research staff on using the lab equipment and handling hazardous reagents.

- Use of Personal Protective Equipment (PPE): Lab coats, gloves, and safety goggles will be worn at all times when handling hazardous reagents. Additional PPE will be used especially when working with viral vectors.

-Work with viral vectors will be conducted in a biosafety level 2 (BSL-2) laboratory to ensure containment and biohazard bags will be used for disposal of contaminated waste materials.

-Biosafety cabinets (BSC) will be used when working with viral vectors and animals to prevent aerosolization and exposure.

-Emergency response protocols, will be established and communicated to all lab members. First aid kits and emergency showers/eyewash stations will be accessible.

- Continuous monitoring of animal models for adverse effects and off-target gene editing and compliance to biosafety levels appropriate for the types of viral vectors and gene – editing tools used will be strictly enforced.

V. Security and Ethics

Ethical considerations are a cornerstone in this research due to the use of gene-editing tools and AI models. Therefore, the following ethical principles will be considered:

- Benefits vs. Risks: Evaluate the potential benefits of treating chronic and treatment-resistant anxiety disorders against the risks involved. The goal is to improve patient outcomes significantly while minimizing harm.

- Ethical approvals will be obtained from relevant institutional review boards.

-Potential ethical issues related to gene editing, such as off-target effects and long-term consequences, will be thoroughly examined.

- Maintain transparency and open communication with the interested parties regarding the study's aims, methods, and potential risks.

- The study will ensure the humane treatment of animal subjects in compliance with the Animal Welfare Act and institutional guidelines.

- Conduct thorough preclinical testing to identify and reduce potential unintended harm and monitor any possible long term effects outcomes before advancing to clinical trials.

- If the research progresses to early-phase clinical trials then informed consent from participants is vital, ensuring patient data will be anonymous to protect their privacy and genetic information will be safe using advanced security protocols to prevent unauthorized access and breaches.

VI. Expected Outcome / Results

- Establishment of a foundational framework for integrating AI with advanced biotechnologies in the treatment of anxiety disorders and potentially other neuropsychiatric conditions broadening the impact of the research.

- Novel and Optimized Treatment Strategies: Development of robust AI models capable of optimizing the delivery of optogenetics and CRISPR-Cas9 systems resulting in the development of innovative treatments and enhanced delivery systems for chronic and treatment-resistant anxiety disorders.

- Identification of Neural Biomarkers: AI analysis of optogenetic data will reveal neural activity patterns associated with anxiety, providing insights into the underlying mechanisms and aiding in the identification of new therapeutic targets.

- Predictive Models for Precision Medicine: Machine learning models that accurately predict patient-specific responses to these therapies, paving the way for personalized treatment plans. These models will be validated and refined through continuous data input and feedback from experimental results.

- Cost-Effective Solutions: Potential reduction in healthcare costs by providing more efficient and targeted treatment options, decreasing the need for multiple or prolonged therapies.

VII. Future Implications

The practical implications of this proposal are profound. Successful completion of the research could revolutionize the treatment of chronic and treatment-resistant anxiety disorders, offering new hope to patients who have not benefited from conventional therapies. By leveraging AI's capabilities with Optogenetics and CRISPR-Cas9 delivery systems we could pave the way for precision medicine approaches in neuropsychiatry, extending to other mental health disorders and neurodegenerative diseases. Furthermore, developing AI-driven personalized treatment plans could enhance the overall efficacy and safety of biotechnological interventions, setting new standards for future research and clinical applications.

VIII. References

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