Personalized Therapeutics for CNS Inflammation and Autoimmune Disorders Using Neo7Logix Precision-Based Immuno-Molecular Augmentation

Md Shamsuddin Sultan Khan [1*], Anton Yuryev [2], John Catanzaro [3]

Abstract

Background: The Precision-Based Immuno-Molecular Augmentation (PBIMA) technology represents an advanced, multi-purpose vaccine design approach, targeting cancer, autoimmune diseases, neurodegenerative disorders, and inflammation-driven conditions. PBIMA utilizes extensive molecular and genetic data to personalize therapy, aiming for enhanced precision and effectiveness. This study explores the application of PBIMA for personalized therapeutic interventions in progressive central nervous system (CNS) inflammation and autoimmune diseases. Methods: PBIMA leverages next-generation sequencing (NGS) data, including whole-exome sequencing (WES), whole-genome sequencing (WGS), and RNA sequencing, to identify genetic predispositions and autoantigens. The technology integrates patient-specific data for designing personalized vaccines through reverse vaccination strategies. This process includes peptide selection from self-antigen sequences and the administration of regulatory T cells and cytokines. Results: Genetic analysis revealed variants associated with autoimmune disorders, particularly affecting the IL6R, IL6ST, and TNFRSF1B genes, linked to demyelination and CSF leaks. The personalized PBIMA approach successfully identified autoantigens and employed reverse vaccination to promote immune tolerance, targeting specific pathways involved in disease progression. Conclusion: The Neo7Logix PBIMA strategy demonstrated potential in personalizing therapy for complex autoimmune conditions involving CNS inflammation. The tailored approach effectively addressed genetic predispositions and autoantigen targets, highlighting the promise of reverse vaccination in managing autoimmune diseases. Future research should refine epitope selection, optimize protocols, and validate efficacy across diverse patient cohorts.

Keywords: Precision Medicine, Neo7Logix PBIMA, Autoimmune Diseases, CNS Inflammation, Reverse Vaccination

Significance | Neo7Logix PBIMA offers a novel, personalized approach to treating CNS autoimmune disorders, enhancing therapeutic precision and efficacy

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1.Introduction

The PBIMA is a promising multipurpose-vaccine design technology that can produce vaccines against cancer, autoimmune disease, neurodegenerative disorders, inflammation-driven diseases, and novel pathogen-mediated infections (Yin, Li, & Li, 2022). The main objective of PBIMA is to enhance the precision and effectiveness of therapy by leveraging molecular and immunological information. The PBIMA is a modern approach involving strategic selection, molecular mapping, antigen alignment, receptor recognition, and tactical technology (Khan, Tang, Wu, & Hauser, 2023). Data from a patient's genes and proteins, especially the NGS data including WES, WGS, ctDNA

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(and/or cfDNA), and RNAseq, are used as input, and high-confidence peptides are selected from a gene-protein-cell cloud-based sequence editing interface connected to PBIMA (Manoharan, Albert, & Powner, 2018). Since PBIMA therapeutic design is multi-mechanistic and broad spectrum, it can be effectively administered in cancer treatment (Lu & Zhang, 2021).

The development of personalized therapeutics using PBIMA Precision Profiling for progressive central nervous system (CNS) inflammation and autoimmune diseases represents a significant advancement in precision medicine (Zhang, Li, & Zhang, 2023). Autoimmune diseases and inflammation-driven conditions, such as Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE), Amyotrophic Lateral Sclerosis (ALS), Scleroderma, Mixed Connective Tissue Disease, Hashimoto's Thyroiditis, Rheumatoid Arthritis, and other related disorders, pose considerable challenges due to their complex and multifaceted pathophysiology (Chen, Ding, Zhang, & Wang, 2022; Crispin & Tsokos, 2020; Barton & Worthington, 2019). Traditional treatments often focus on symptomatic management, which may not address the underlying mechanisms driving disease progression (Noster, Wahren, Meisel, & Oertelt-Prigione, 2021). Neo7logix Precision-Based Immuno-Molecular Augmentation (PBIMA) offers a novel approach that aims to personalize therapy by leveraging advanced molecular profiling techniques to design treatments tailored to the specific needs of each patient (Neo7 Bioscience, Inc., 2022, Neo7Logix, LLC. 2023).

In this study, we aimed to develop personalized therapy for progressive CNS inflammation and autoimmune diseases using Neo7logix precision profiling. The target patient is a female over 50 years old with a complex clinical presentation, including a CNS syrinx, neuronal inflammation, and autoantibody reactivity. Her symptoms include progressive intermittent seizures, fluid leakage from multiple sites (ears, eyes, nose, throat), and global fatigue and weakness (Galeotti & Kaveri, 2020). These symptoms suggest underlying autoimmune pathology that requires a targeted and personalized therapeutic strategy (Abele & Schlegel, 2017).

The PBIMA approach facilitates personalized treatment through reverse vaccination, which can suppress autoimmunity by either inducing the deletion of naïve T cells specific to vaccine peptides or promoting the differentiation of regulatory T cells (Dai & Wang, 2021; Sabatino, Pröbstel, & Zamvil, 2019) (Figure 1). These regulatory T cells have the capacity to inhibit pathogenic inflammatory memory T cells (Th1) and prevent the activation of naïve T cells against self-antigens released during tissue damage via epitope spreading (Renoux, Motsch, & Kuchroo, 2020). Furthermore, PBIMA can directly induce anergy at the level of memory T cells and promote clone deletion (Dendrou, Fugger, & Friese, 2018). Targeted immunosuppression is a critical component of this strategy, aiming to deactivate the immune system's attack on the patient's organs (Orlowski, Colonna, & Xu, 2018). This deactivation targets specific proteins recognized by autoantibodies or memory T cells, which may be secreted by the affected organs or present on the plasma membranes of damaged tissue cells (Albini, Bruno, Noonan, & Mortara, 2018).

To achieve effective targeted immune suppression, the process begins with analyzing the patient's genotype using whole-exome sequencing (WES) to identify proteins encoded by homozygous alleles that are associated with the autoimmune disease (Wu, Alvarez, & Glasier, 2018). Potential autoantigens are then identified, and peptides are calculated from self-antigen sequences for administration, accompanied by physiological immunosuppressors such as cytokine IL10 or CD25+ regulatory T lymphocytes (Schett, Gravallese, & Miossec, 2017). This ensures the production of soluble major histocompatibility complex (MHC) molecules bound to peptides from the vaccine, which can down-regulate memory T cells and B cells, thereby mitigating the autoimmune response (Cossarizza et al., 2017).

In this study, we focus on two primary pathological processes in the patient: spontaneous cerebrospinal fluid (CSF) leaks and demyelination (Gonzalez, Robles, & Ibanez, 2023). CSF leaks are considered a result of a recessive genetic predisposition for weak dura mater, potentially exacerbated by an autoimmune response to structural components of the dura mater (Gieseler & Lünemann, 2021). Demyelination symptoms are secondary to the CSF leaks and likely driven by an autoimmune reaction induced by CSF material (Miklossy, 2019). Genetic analysis identified alleles predisposing the patient to autoimmune disorders, and further investigations highlighted specific proteins linked to demyelinating conditions and structural weaknesses in the dura mater (Elliott & Fassas, 2019).

This study demonstrated the potential of Neo7logix precision profiling to identify and target the underlying mechanisms of autoimmune diseases and inflammation-driven CNS disorders, offering a promising approach for developing personalized therapeutics (Sabatino, Pröbstel, & Zamvil, 2019). By leveraging advanced molecular and genetic data, PBIMA can provide tailored interventions that directly address the unique pathophysiology of each patient, potentially improving outcomes and reducing the burden of these challenging conditions (Lu & Zhang, 2021).

2. Materials and Methods

The PBIMA approach utilizes a modern, multi-step process that involves strategic selection, molecular mapping, antigen alignment, receptor recognition, and tactical technology integration (Khan et al., 2023; Neo7 Bioscience, Inc., 2022). Patient-specific genetic and proteomic data, particularly from next-generation sequencing (NGS) methods such as whole-exome sequencing (WES), whole-genome sequencing (WGS), circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), and RNA sequencing (RNAseq), serve as the

primary input (Lu & Zhang, 2021; Zhang et al., 2023). These data are processed through a cloud-based sequence editing interface connected to the PBIMA platform, where high-confidence peptides are selected based on gene-protein-cell interactions (Manoharan et al., 2018).

This multi-mechanistic design leverages a broad spectrum of molecular data to create tailored therapeutic interventions. By aligning antigens with the patient's immune receptors, PBIMA provides a precision-based, personalized therapeutic strategy suitable for cancer treatment. The technology allows for adaptive and targeted responses, ensuring effective clinical outcomes (Neo7 Bioscience, Inc., 2022; Yin et al., 2022).

2.1 Patient Data Input and Sample Collection

Patient data input begins with the collection of biological samples by clinicians. These samples include blood, urine, and tissue, either newly obtained or retrieved from existing stored specimens in hospital biobanks or through next-generation sequencing (NGS) vendors. Once collected, these samples are sent to a designated laboratory for genetic and protein analysis. In the laboratory, the data undergoes a detailed genetic and proteomic evaluation, which is then packaged for further precision mapping.

2.2 Data Upload and Processing

The processed patient data is imported or uploaded into the PBIMA (Precision-Based Immuno-Molecular Augmentation) user interface via a secure website. This data typically includes NGS OMICS data, such as Variant Call Format (VCF) files, which are analyzed using specialized tools within the PBIMA system. The system incorporates tools like the Susceptibility Tool and the Peptide Analysis Tool, which utilize databases such as the MHC Class II Prediction Database and the Immune Epitope Database (IEDB). The outputs are peptide sequences of 10-20 amino acids, formatted in tab-separated value (TSV) files or other compatible formats. These sequences are then subjected to CRISPR editing to achieve the desired genetic modifications.

2.3 Cloud-Based Sequence Editing and Data Cataloging

The PBIMA system operates on a cloud-based sequence editing API, which receives data files over a secure network from hospitals, clinicians, or NGS vendors. The API facilitates the input, processing, and analysis of data without the need for additional biological sample preparation steps by the vendors. Data files, such as fastq and BAM files containing raw sequencing data, are first analyzed in the PBIMA application to generate outputs for subsequent processing stages.

The PBIMA system employs scripts to process VCF files by identifying sequences around somatic mutations found in normal and tumor cells. Whole-exome sequencing (WES) data from NGS vendors is also integrated, providing a comprehensive genomic analysis tailored to the patient's clinical context.

2.4 Precision Mapping and Peptide Selection

The next step involves precision mapping and selection, where the patient's data is analyzed to evaluate their immune defense status and identify specific disease processes. This mapping is conducted using PBIMA, a platform that designs vaccine compositions containing multiple peptides that encode antigens to stimulate the patient's immune system against the disease. The platform employs various open-source and proprietary software tools, such as the Genome Uniqueness Tool and the Gene-Protein-Disease Interaction Database, to refine the selection of target peptides.

2.5 Neoantigen Identification and Ranking

The PBIMA system further analyzes the data to identify self-antigens and neo-antigens for immunomodulation. For cancer patients, CD8+ cell-modulating neo-antigens are identified, while for autoimmune conditions, CD4+ cell-modulating antigens are determined. The selected peptides are ranked based on multiple criteria, including patient-specific transcriptomics and proteomics data, relevant literature, cancer hallmark collections, and manufacturability considerations.

2.6 Vaccine Design

The final output includes a ranked list of peptides, which are then synthesized for vaccine development. The peptides, generally ranging from 9 to 20 amino acids, are specifically chosen to engage MHC Class I and II pathways. These peptides are designed to modulate immune responses effectively, based on the unique genetic and proteomic profile of each patient, as determined by the PBIMA system.

2.7 Data Integration and Analysis Tools

Throughout the process, the PBIMA platform integrates a range of data inputs, including NGS OMICS files, proteomics data, and various peptide analysis tools. The system's Unification API can convert or prepare the necessary file formats for input, ensuring seamless data processing and analysis. By leveraging cloud-based databases and APIs, PBIMA provides a robust framework for the identification, design, and manufacture of personalized immunotherapies.

3.Results

3.1 Identification of Genetic Predispositions to Autoimmune Disorders and Inflammatory Processes

Whole exome sequencing (WES) analysis of the patient's genome revealed several genetic variants (GVs) associated with autoimmune disorders and inflammatory processes. The identified homozygous variants, including those in the *IL6R*, *IL6ST*, and *TNFRSF1B* genes, are involved in demyelination and expressed on astrocytes (Figure 2). These genes are essential for the structural integrity of the myelin sheath and the maintenance of the blood-brain barrier, making them potential targets for immune-mediated attacks in demyelinating and psychiatric disorders. The presence of these alleles indicates a genetic susceptibility to autoimmune

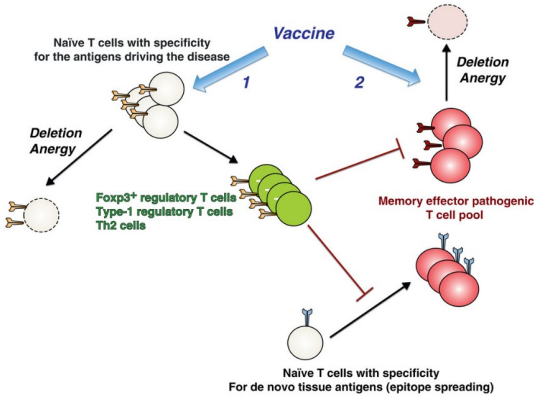

Figure 1. Suppressing autoimmunity by reverse vaccination

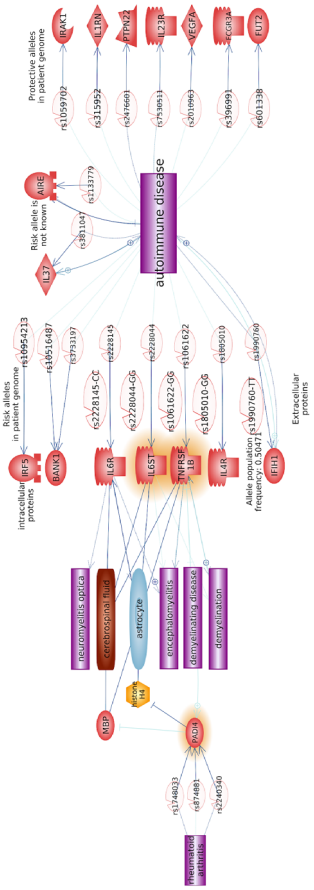

Figure 2. Genes with genotypes predisposing patient to autoimmune disease and their links to demyelinating disorders. Proteins found in patient urine are shown by orange highlight

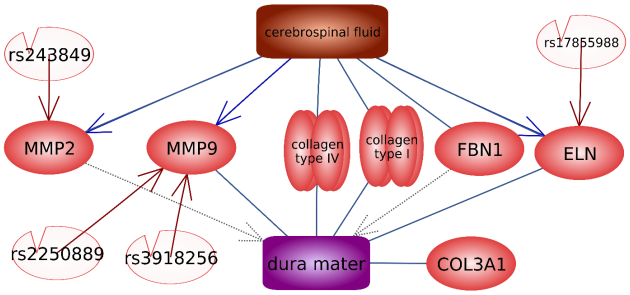

Figure 3. Extracellular matrix proteins expressed in dura mater. (GV homozygous in patient's genome are linked to dura mater structural proteins.)

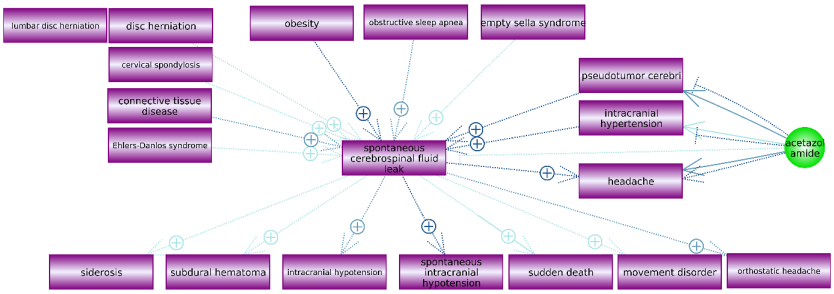

Figure 4. Diseases linked to spontaneous CFS leaks in Pathway Studio Knowledge-Base

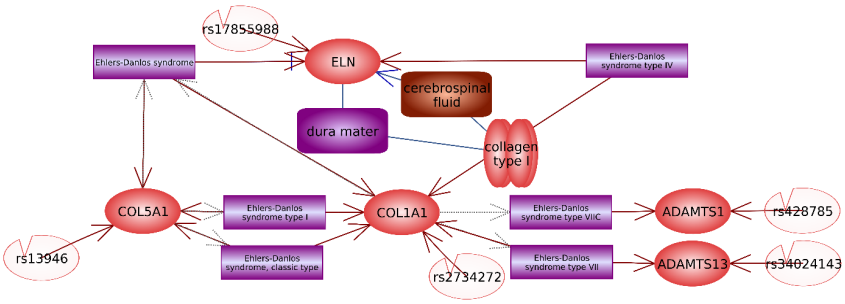

Figure 5. Proteins linked to Ehlers-Danlos syndrome that are homozygous in patient's genome.

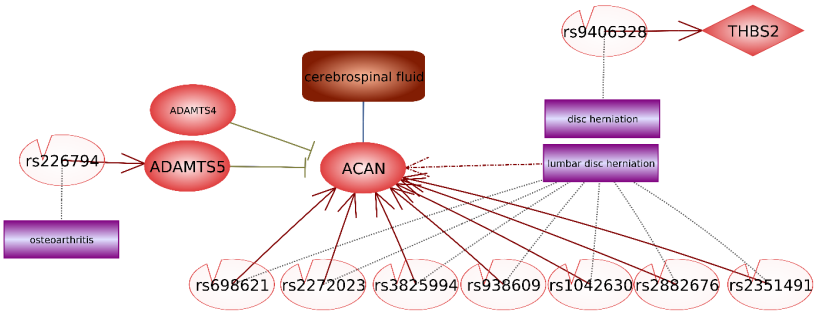

Figure 6. Proteins linked to disk herniation that are homozygous in patient's genome.

Table 1. Homozygous proteins selected for epitope calculation

Protein	Localization	Diseases linked
IL6R	Plasma membrane, CSF, astrocytes	Demyelination, autoimmunity
IL6ST	Plasma membrane, CSF, astrocytes	Demyelination, autoimmunity
TNFRSF1B	Plasma membrane, CSF, astrocytes	Demyelination, autoimmunity
IL4R	Plasma membrane, soluble receptor	autoimmunity
IFIH1	Plasma membrane, intracellular	autoimmunity
COL1A1	Dura mater, CSF	Autoimmunity, Ehlers-Danlos syndrome
COL3A1	Dura mater, CSF	Autoimmunity
COL4A1	Dura mater, CSF	Autoimmunity
COL5A1	Dura mater, CSF	Autoimmunity, Ehlers-Danlos syndrome
FBN1	Dura mater, CSF	Autoimmunity
ELN	Dura mater, CSF	Autoimmunity, Ehlers-Danlos syndrome
ACAN	Dura mater, CSF	Autoimmunity, disk herniation

Table 2. Lists the PBIMA designed neoantigens (proteins) and self-antigens (proteins) and Immunopeptide sequences for a Progressive CNS Inflammation Autoimmune Disease patient diagnosed and treated using the present invention method and system. The final selection of proteins was sorted according to their rank and their peptide with the best affinity towards the patient's MHC-I complexes.

SEQ ID NO:	Autoimmune peptide sequences
13	WSREEQEREE
14	ADIYTEEAGR
15	NAPVSIPQ
16	SALLRSIPA

Table 3. Lists of PBIMA designed neoantigens (proteins) and self-antigens (proteins), and Immunopeptide sequences for another Progressive CNS Inflammation Autoimmune Disease patient diagnosed and treated using the present invention method and system. The final selection of proteins was sorted according to their rank and their peptide with the best affinity towards the patient's Citrullinated MHC Class-II complexes.

SEQ ID NO:	Protein	Sequence
17	MBP-R25	YLATASTMDHA(cit)HGFLPRHRDTG
18	MBP-R49	LDSIGRFFGGD(cit)GAPKRGSGKVP
19	MBP-R122	DENPVVHFFKNIVTP(cit)TPPPSQGKGRG
20	MBP-R130	PRTPPPSQGKG(cit)GLSLSRFSWGA
21	MBP-R122/R130	P(cit)TPPPSQGKG(cit)G

diseases, which could contribute to the observed cerebrospinal fluid (CSF) leaks and neuronal inflammation.

3.2 Autoantigen Identification and Targeted Immune Suppression

The patient presented with two primary pathological processes: spontaneous CSF leaks and secondary demyelination with blood-brain barrier breakdown. The spontaneous CSF leaks were hypothesized to result from a genetic predisposition for weakened dura mater, potentially exacerbated by an acquired autoimmune response targeting structural components of the dura. This hypothesis was supported by the identification of extracellular matrix (ECM) proteins linked to the dura mater's structural integrity and associated with genetic predispositions for connective tissue disorders, such as Ehlers-Danlos syndrome, cervical spondylosis, and disc herniation (Table 2, Table 3, Figure 4, Figure 5).

To suppress autoimmunity, a personalized therapeutic approach utilizing the Neo7Logix Precision-Based Immuno-Molecular Augmentation (PBIMA) was implemented. Peptides derived from self-antigen sequences were administered with cytokine IL10 and CD25+ regulatory T-lymphocytes, isolated and expanded from the patient's blood in vitro. This strategy aimed to induce immune tolerance by promoting the deletion or anergy of pathogenic memory T cells, thereby reducing the autoimmune attack on target tissues. The therapeutic method also employed soluble MHC molecules to downregulate B cells and T cells activated in response to the patient's autoimmune condition, mitigating the pathological inflammatory response (Table 1).

3.3 Analysis of Potential Autoantigens in the Patient

The search for potential autoantigens revealed several proteins secreted into the CSF, such as those involved in astrocyte function and the integrity of the blood-brain barrier. The identified genes—*IL6R*, *IL6ST*, and *TNFRSF1B*—were linked to demyelination disorders and expressed on astrocytes, crucial for maintaining myelin integrity around neurons. The presence of these genes suggests that the patient's immune system may be targeting these astrocytes, contributing to the breakdown of the blood-brain barrier and exacerbating neuroinflammation (Figure 2).

Additionally, the ECM proteins contributing to the structural integrity of the dura mater were examined, revealing a predisposition to spontaneous CSF leaks. Analysis of the patient's genetic data identified proteins associated with connective tissue disorders known to cause structural weaknesses in the dura mater, such as Ehlers-Danlos syndrome (Figure 5). This finding supports the hypothesis that autoimmune processes contribute to the patient's clinical presentation.

3.4 Epitope Prediction for Reverse Vaccination

Epitopes from extracellular regions of proteins associated with the patient's autoimmune condition were identified using the Immune Epitope Database (IEDB) along with the patient's HLA types. These epitopes were selected for developing a personalized reverse vaccination protocol aimed at inducing immune tolerance (Table 1). The reverse vaccination strategy aimed to promote the deletion of autoreactive T cells and inhibit the autoimmune response, reducing the severity and progression of the disease.

4. Discussion

The results underscore the potential of personalized therapeutic approaches, such as the Neo7Logix PBIMA method, to address complex autoimmune conditions involving central nervous system (CNS) inflammation and neuronal damage (Khan et al., 2023; Neo7 Bioscience, Inc., 2022). The identification of specific genetic predispositions and autoantigen targets enabled a tailored immunosuppressive strategy to modulate the patient's immune response and reduce pathological inflammation (Galeotti & Kaveri, 2020; Zhang et al., 2023).

The detection of key autoantigens associated with CNS inflammation emphasizes the complexity of autoimmune diseases, where multiple genetic and environmental factors converge to produce a clinical phenotype (Chen et al., 2022; Gonzalez et al., 2023). In this case, the presence of genetic variants associated with autoimmune disorders and demyelination suggests a multifaceted etiology, involving both structural defects and immune dysregulation (Dendrou et al., 2018; Renoux et al., 2020). These findings highlight the importance of considering genetic predispositions when developing personalized therapies for patients with autoimmune conditions, particularly those affecting the CNS (Albini et al., 2018; Cossarizza et al., 2017).

The use of a reverse vaccination strategy to suppress autoimmunity represents a promising approach for targeting specific pathways involved in disease progression (Elliott & Fassas, 2019; Noster et al., 2021). By promoting immune tolerance through the induction of regulatory T cells and deletion of autoreactive T cells, the reverse vaccination protocol offers potential long-term benefits in managing autoimmune conditions (Sabatino et al., 2019; Wu et al., 2018). These findings support further exploration of this approach in a broader cohort of patients to validate its efficacy and safety (Yin et al., 2022; Miklossy, 2019).

Future research should focus on refining the epitope selection process, optimizing the reverse vaccination protocol, and investigating the long-term outcomes of patients treated with this personalized approach (Manoharan et al., 2018; Orlowski et al., 2018). Additionally, expanding the patient cohort to include individuals with varying genetic backgrounds and disease manifestations will help to better understand the applicability and generalizability of the Neo7Logix PBIMA strategy in treating autoimmune diseases with CNS involvement (Barton & Worthington, 2019; Crispin & Tsokos, 2020).

Author contributions

A.Y., M.S.S.K. analyzed the data, conducted the experiments. M.S.S.K. wrote and revised the manuscript, J.C. revied the draft. All authors reviewed and approved the final version of the manuscript for publication.

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Competing financial interests

The authors have conflict of interest. M.S.S.K. and J.A.C. are employee of Neo7bioscince and M.S.S.K. is the director of Eman Research.

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