GSC Advanced Research and Reviews
eISSN: 2582-4597 CODEN (USA): GARRC2
Cross Ref DOI: 10.30574/gscarr
Journal homepage: https://gscarr.gsconlinepress.com/

(REVIEW ARTICLE)

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CD23 IN PARKINSON'S DISEASE: RATIONALE AND CHALLENGES FOR EXPLORING PREFORMED ANTI-IGE:IGE COMPLEXES

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GSC Advanced Research and Reviews, 2026, 29(01), 265–269

Publication history: Received on 12 September 2026; revised on 18 October 2026; accepted on 20 October 2026

Article DOI: https://doi.org/10.30574/gscarr.2026.29.1.0285

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder for which available treatments are primarily symptomatic. Neuroimmune changes are implicated in PD, and experimental work has reported CD23 (FcεRII) expression in glial cells and CD23-associated inflammatory mediator production *in vitro*. These findings provide a rationale for investigating CD23, but they do not establish that CD23 drives disease progression or that its modulation is therapeutic. This hypothesis-generating review considers whether a preformed anti-IgE antibody–IgE complex, such as UB-221 (also referred to as CUE-221), could alter CD23-associated signaling in PD. The proposed effects on glia, NOS2, and neuronal injury remain untested, as does the complex's ability to reach relevant brain compartments. Potential delivery approaches—including receptor-mediated transport and focused ultrasound—are discussed as research options rather than established solutions. Preclinical studies should first determine target expression, complex behavior and safety, functional effects in relevant PD models, and brain exposure. CD23-directed immunomodulation is therefore a speculative research hypothesis, not an established disease-modifying strategy.

Keywords: Parkinson's Disease, Neuroinflammation, Immunotherapy, CD23, Preformed CUE22: Ige, B-Cell Modulation

1 INTRODUCTION

Parkinson's disease is a prevalent neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons and persistent neuroinflammation [1,2]. While current therapies provide symptomatic relief, they do not halt or reverse disease progression, largely because of the intricate interplay between the immune system and neuronal health [1,2]. Recent research highlights the pivotal role of immune dysregulation, particularly involving microglia, astrocytes, and B cells, in driving chronic inflammation in PD [1,2]. This review explores an immunotherapeutic approach that targets the low-affinity IgE receptor CD23 using preformed CUE-221:IgE complexes. Related reviews have proposed CD23-engaging anti-IgE:IgE complexes for immune modulation in cystic fibrosis [3], refractory autoimmune diseases [4], giant cell myocarditis [5], and neonatal sepsis [6]. This hypothesis extends this platform to Parkinson's disease, where brain-associated microglia, astrocytes, and B cells remain untested targets of CD23-modulating complexes [7,8].

2 DISCUSSION

Abnormal upregulation of CD23 (FcεRII) in the brain contributes to the chronic neuroinflammation and oxidative stress that drive dopaminergic neuron loss in Parkinson's disease (PD) [7,8]. Unlike healthy brain tissue, which lacks detectable CD23 expression, glial cells in the substantia nigra of PD patients show marked increases in this receptor [7]. This pathological shift highlights CD23 as a promising therapeutic target for modulating neuroinflammatory cascades and potentially altering disease progression [7,8].

2.1 Optimizing Preformed CUE-221:IgE Complexes for Therapeutic Applications

CUE-221 (also known as Ascendant-221 or UB-221) is a humanized anti-IgE IgG1 monoclonal antibody [9,10,16]. A preformed CUE-221:IgE complex forms when the CUE-221 antibody binds to exogenous Immunoglobulin E (IgE) molecules. The precise IgE component of the CUE-221:IgE complex for neurological use is preferably a recombinant, non-allergenic IgE to reduce immune activation risks.

The intended preformed CUE-221:IgE complex is a stoichiometric antibody–antigen complex in which each IgG1 (CUE-221) molecule binds to an exogenous IgE.

Humanized or fully human sequence (exogenous IgE) to reduce immunogenicity.

- Non-allergenic (non-specific to known environmental or food allergens).
- High structural stability and purity to ensure reliable complex formation with CUE-221.
- Validated low risk of spontaneous mast cell or basophil activation in preclinical safety studies.
- Preferably a monoclonal IgE with a known, inert antigen-binding fragment (such as a specificity for a synthetic or irrelevant hapten not found in humans).

Future research should clarify which molecular features of preformed anti-IgE:IgE complexes minimize effector cell activation while retaining CD23 engagement.

2.2 Mechanistic Hypotheses: Potential Effects of Preformed CUE-221:IgE Complexes on NOS2 and Glial Activation [7,8,12]

CUE-221 (formerly UB-221) is a next-generation, humanized anti-IgE monoclonal antibody with a unique mechanism of action. Unlike earlier anti-IgE therapies such as omalizumab, which inhibit all IgE-CD23 interactions, preformed CUE-221:IgE complexes may selectively bind to CD23 on brain-associated microglia, astrocytes, and B cells. The following mechanisms are hypotheses based on in vitro data and have not been demonstrated in the context of Parkinson's disease or in vivo models:

2.2.1 Hypothetical Mechanism A: Steric Blockade and Competitive Antagonism by Preformed Anti-IgE:IgE Complexes

When CUE-221: IgE complexes bind CD23, the structural bulk of these complexes can alter receptor behavior [11,16]

- Prevention of Cross-linking: High-output NOS2 activation is hypothesized to require multimeric cross-linking of surface CD23 receptors, but this pathway has not been established in vivo. [11,12]
- Inert Binding: It is hypothesized that the CUE-221:IgE complex could bind CD23 in a way that physically blocks pathological antigens—such as environmental neurotoxins or allergens—from cross-linking the receptor, thereby acting as a competitive antagonist; this has not been demonstrated experimentally.
- The Downstream Effect: If receptor aggregation or cross-linking is prevented, downstream signaling pathways such as NF-κB or MAP kinase might remain inactive, potentially limiting NOS2 induction and subsequent nitric oxide production; this outcome remains unproven in vivo.

2.2.2 Hypothetical Mechanism B: Inducing Negative Feedback and Homeostatic Signaling via Preformed CUE-221:IgE Complexes

In B cells, CUE221:IgE complexes bind to CD23 and may activate a natural negative-feedback loop that suppresses additional IgE synthesis [9,10,16]. In glial cells, it is hypothesized that this interaction may promote a homeostatic or anti-inflammatory state and reduce pathological activation, but this effect has not been established in vivo [7,8,12].

- Shifting Glial Phenotypes: It is hypothesized that directing CD23 into a regulatory rather than pro-inflammatory conformation may help maintain glial cells in a quiescent, neuroprotective state; this has not been demonstrated.

- Transcriptional Suppression: By preventing activation of key pathways such as JAK-STAT and NF-κB, the CUE-221:IgE complex is hypothesized to suppress NOS2 gene expression, maintain low nitric oxide levels, and protect neurons from oxidative damage; these outcomes require experimental validation [12].

A major translational challenge is delivering large macromolecular complexes such as preformed CUE-221:IgE across the blood-brain barrier (BBB). Monoclonal antibodies and antibody-antigen complexes are typically too large to diffuse passively, so they require active transport or physical disruption strategies to reach therapeutic concentrations in the brain [15,16].

The primary scientific strategies capable of trafficking these specific macromolecular complexes into the brain include:

2.3 Possible Strategies for Brain Delivery of Preformed CUE-221:IgE Complexes

One possible approach based on general news is to engineer the antibody or complex to target endogenous receptors on brain capillary endothelial cells, such as the transferrin receptor (TfR) or insulin receptor (IR), to facilitate receptor-mediated transcytosis [14,15]. This strategy has been demonstrated for certain biologics, but its applicability to preformed CUE-221:IgE remains untested. The cited insulin-receptor reference is limited to receptor biology and does not establish BBB delivery for this complex.

- Transferrin or Insulin Receptor Shuttles: Monovalent "brain shuttle" arms that target the transferrin or insulin receptor [18] are being studied to enhance brain delivery of biologics. Whether this method would deliver intact preformed CUE-221:IgE complexes to relevant brain regions is unproven and requires empirical investigation.
- Monovalent Binding Optimization: As detailed in biotech transport research, the shuttle arm must engage the BBB receptor with moderate, monovalent affinity. High-affinity bivalent binding will cause the receptor-complex unit to mis-sort into the endolysosomal compartment for degradation inside the cell rather than releasing it into the brain parenchyma [15].

2.4 Leveraging CD23 Pathway: Harnessing Preserved Receptor Interactions for Targeted Delivery

A unique attribute of CUE-221 is its precise engineering: unlike omalizumab, CUE-221 preserves the Anti-IgE:IgE complex's ability to bind the low-affinity CD23 receptor (FcεRII) [19,6].

- CD23-Mediated Transcytosis: In certain tissues, CD23 serves as a bidirectional transporter for IgE and its complexes. It is unknown whether brain endothelial cells express sufficient functional CD23 to mediate transport of preformed CUE-221:IgE complexes during neuroinflammation. This pathway remains theoretical and has not been demonstrated for brain delivery.

2.5 Focused Ultrasound (FUS) and Microbubbles: Transiently Opening the BBB for Targeted Delivery

If modifying the preformed CUE221:IgE complex compromises its dual mechanism, transient physical opening of the BBB—such as by focused ultrasound (FUS) with microbubbles—has been proposed as an alternative route. This technology enables temporary and localized BBB disruption to allow entry of large molecules, but its safety and efficacy for delivering CUE-221:IgE are untested.

- When combined with systemic microbubble injection, localized Focused Ultrasound (FUS) can temporarily open BBB tight junctions in targeted brain regions. This approach permits large proteins and intact immune complexes to enter the brain parenchyma before the barrier reseals.

2.6 Nanoparticle Encapsulation: Enhancing Brain Delivery of Preformed CUE-221:IgE Complexes

- Encapsulating preformed CUE-221:IgE complexes in polymeric nanoparticles, liposomes, or lipid nanoparticles coated with BBB-targeting ligands (such as apolipoprotein E for LRP1 targeting) has been studied for other therapeutics. The ability of such systems to deliver functional preformed CUE-221:IgE to relevant brain compartments remains unproven and requires dedicated preclinical study.

3 CONCLUSION

Targeting CD23 with preformed CUE-221:IgE complexes offers a compelling, innovative immunotherapy approach for Parkinson’s disease. By modulating neuroinflammation through competitive antagonism and restoring homeostatic signaling, this strategy addresses a central driver of neuronal degeneration. While significant translational hurdles remain—particularly in delivering macromolecular therapies across the blood-brain barrier—the mechanistic rationale and available findings justify testing this hypothesis in appropriate preclinical models; efficacy and feasibility remain

unknown. Ultimately, CD23-based immunomodulation could shift the therapeutic paradigm, offering hope for disease modification in Parkinson's disease and advancing our understanding of neuroimmune interactions in neurodegeneration.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

Michael John Dochniak used artificial intelligence technology to prepare this review article. Mr. Dochniak used Gemini AI (version 2.5 Pro, Google LLC, Mountain View, CA) and Perplexity during the October 2026 research period. Dochniak did not use the tool to generate original scientific content. The author takes full responsibility for the integrity of all content generated and presented in this review article.

Michael John Dochniak used the program "Grammarly" for grammar, spelling, and punctuation throughout the preparation of the review article. Mr. Dochniak used Grammarly, version 14.1271.0 (Grammarly Inc., San Francisco, CA). Dochniak used Grammarly to review and edit the entire article for grammatical accuracy, clarity, and readability. Grammarly's AI-powered writing assistant suggested improvements to sentence structure, word choice, and tone consistency, which the author reviewed and selectively incorporated. The author did not use it to generate original scientific content or research conclusions. The author takes full responsibility for the integrity of all content generated and presented in this review article.

Disclosure of conflict of interest

The author claims no conflict of interest.

Author Profile

Michael John Dochniak is an independent medical researcher who has authored several books on Alzheimer's disease, Artificial Intelligence, Autism Spectrum Disorders, and Climate Change through Cambridge Scholars Publishing and Nova Science Publishers. Mr. Dochniak has also written extensively with GSC Online Press and appreciates its dedicated service.

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