

Engineering an Optimized IgG3 Antibody for Alzheimer's Disease

Overcoming Native IgG3 Limitations Through Rational Antibody Engineering



Uday Chinnappa Marisuse, Medicine, AMA School of Medicine, Makati City, Philippines

CLINICAL NEED	QUESTION & OBJECTIVES	METHODOLOGY	RESULTS OF DESIGN ANALYSIS
Current anti-amyloid therapies remove plaques but demonstrate modest clinical benefit.^{1,2} Existing options fail to fully address tau pathology, blood-brain barrier (BBB) penetration, or overall chronic neuroimmune dysfunction.³	Research Question: Can rational engineering overcome the intrinsic limitations of native IgG3 and create a multifunctional antibody platform for Alzheimer's disease? Objectives: Enhance half-life Improve BBB transport Enable dual Aβ/Tau targeting Maintain potent immune clearance	Literature-Based Antibody Engineering Framework Reviewed: - IgG subclass biology - Fc engineering strategies - BBB shuttle technologies - Bispecific antibody platforms - Alzheimer's immunotherapy	Five major native IgG3 limitations were structurally identified: - Short serum half-life - Structural instability (extended hinge region) - Excess non-specific inflammation - Limited BBB penetration - Single-pathology targeting These specific parameters directly guided the engineered design layout.

Why IgG3?		
Feature	IgG1	IgG3
Fc Binding	Moderate	Highest
Complement Activation	Moderate	Highest
Phagocytosis	Moderate	Highest
Microglial Engagement	Moderate	Highest
Key Advantages		
Strongest Fcγ receptor binding profile Potent classic complement activation pathways Enhanced microglial phagocytosis & clearance kinetic values		

Anti-Aβ Fab

Targets aggregated amyloid-β species

- Oligomers
- Protofibrils
- Plaques

Anti-Tau Fab

Targets pathological tau species

- Phosphorylated tau
- Tau aggregates
- Neurofibrillary tangles

ENGINEERED IgG3

BISPECIFIC TARGETING

Simultaneous binding to Aβ and Tau pathologies

ENHANCED CLEARANCE

Promotes removal of plaques and tangles

BBB PENETRATION

Improved delivery to the central nervous system

EXTENDED HALF-LIFE

Sustained therapeutic exposure

POTENT IMMUNE ACTIVATION

Strong microglial engagement and complement activation

Dual Targeting

Aβ + Tau

+

BBB Shuttle

Enhanced CNS Delivery

+

Extended Half-Life

LS Mutation

+

Potent Fc Function

Fc Optimization

=

Enhanced Pathological Clearance

Better Outcomes

A Next-Generation IgG3 Platform for Comprehensive Alzheimer's Disease Therapy

Design Strategy Cascade

Native IgG3 → Identify Limitation → Engineer Solution → Expected Benefit

ENGINEERING SOLUTIONS		
Native Limitation	Engineered Solution	Expected Clinical Benefit
Short Half-life	LS Mutation	Extended Serum Half-life
Inflammation	Fc Tuning	Controlled Microglial Activation
BBB Penetration	BBB Shuttle Integration	Enhanced CNS Delivery Kinetics
Single Target	Bispecific Arm Design	Dual Aβ + Tau Clearance
Proteolytic Susceptibility	Hinge Stabilization	Improved Structural Stability