

A Novel ELISA for Semi-Quantitative Detection of IgG, IgA, and IgM Autoantibodies Targeting the N-terminal Domain of the GluN1 Subunit of NMDA Receptors in Neuropsychiatric and Neurologic Disorders

TU192

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Anti-NMDA receptor GluN1 autoantibodies have been widely detected in neuropsychiatric and dementia patients (but WHY?)

Anti-NMDA Receptor Encephalitis (ANRE)

Symptoms

- Hallucinations, psychosis, cognitive dysfunction, seizures, dysautonomia, coma, and respiratory failure

Cause

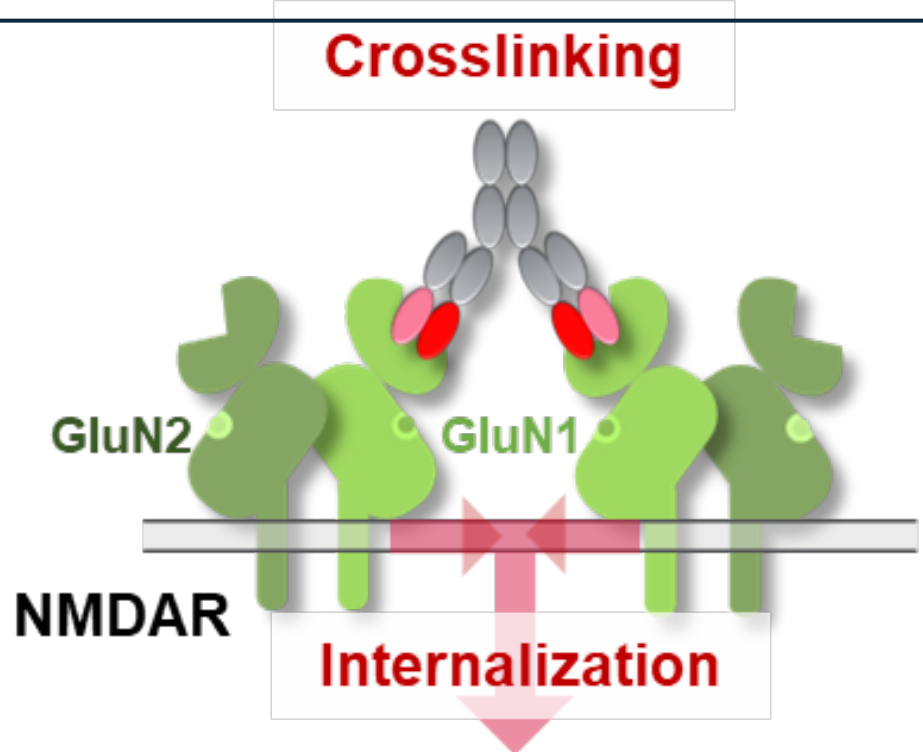
- Autoantibodies (autoAbs) against NMDA receptor (NMDAR)
- Triggered by tumors (paraneoplastic-mainly ovarian teratomas) and herpes simplex encephalitis, or unknown origin

Disease Mechanism

- AutoAbs (two-armed IgG) bind to **selective epitopes** in N-terminal domain (NTD) of NMDAR GluN1 subunit
- Cross-linking of NMDARs triggers their internalization leading to **hypo-NMDAR status**

Standard of Care

- 1st line: Steroids, IVIg, Plasma Exchange
- 2nd line: Rituximab, Cyclophosphamide



Influence of methodological and patient factors on serum NMDAR IgG antibody detection in psychotic disorders: a meta-analysis of cross-sectional and case-control studies

Lancet Psychiatry 2021; 8: 109–20

Psychosis / Schizophrenia

Dynamic disorganization of synaptic NMDA receptors triggered by autoantibodies from psychotic patients

NATURE COMMUNICATIONS
DOI: 10.1038/s41467-017-01700-3

High prevalence of NMDA receptor IgA/IgM antibodies in different dementia types

Annals of Clinical and Translational Neurology 2014; 1(10): 822–832

Dementia

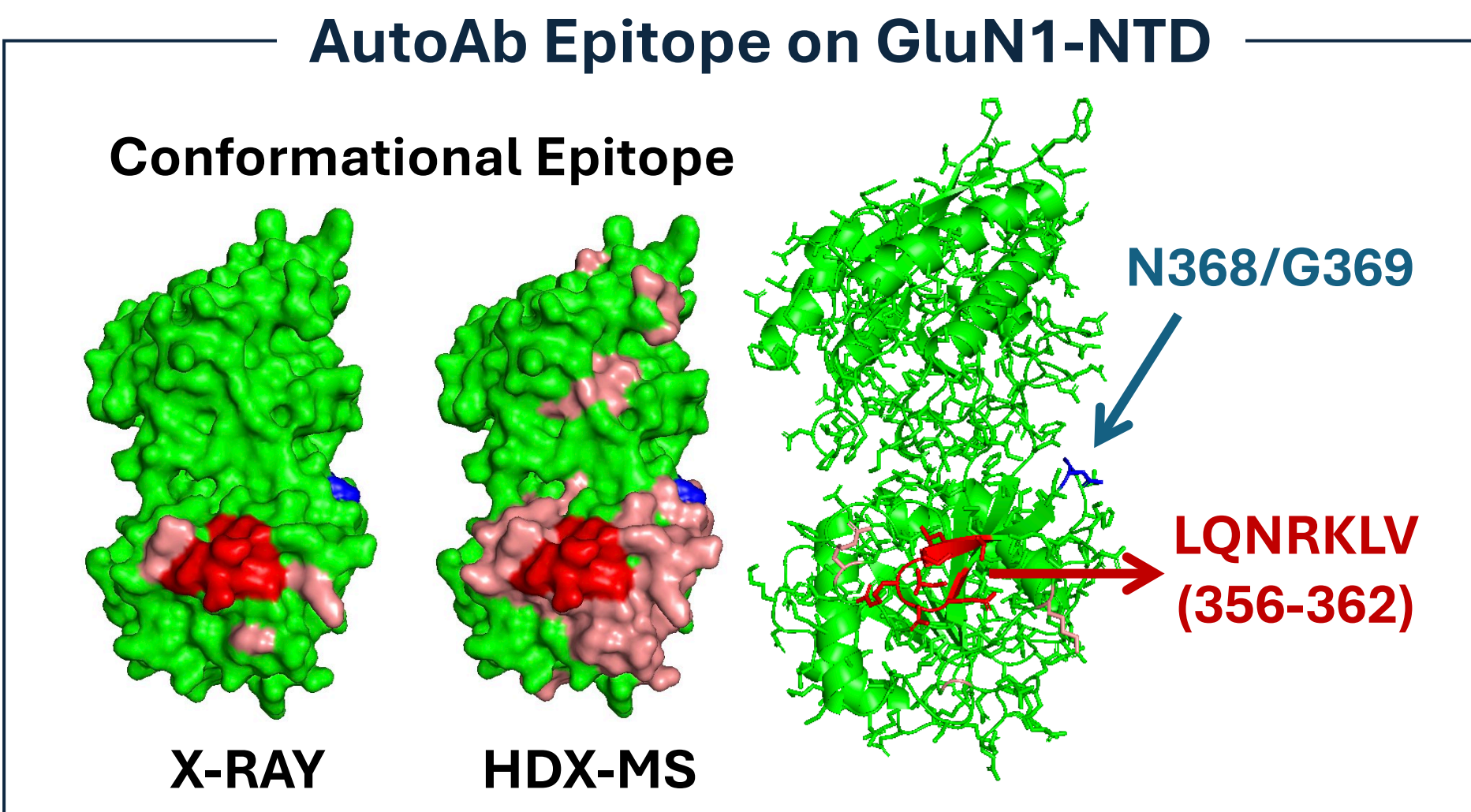
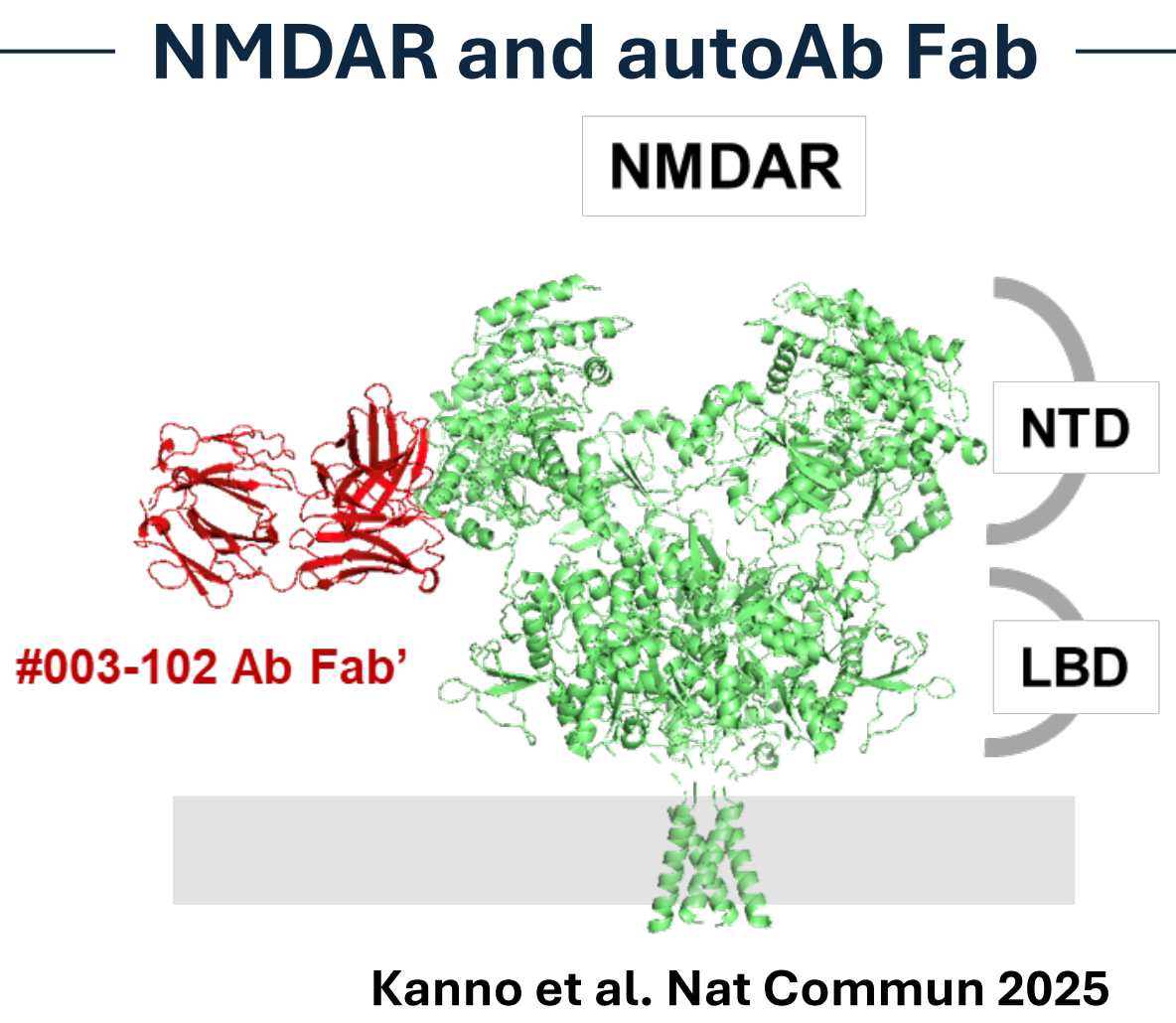
High prevalence of neuronal surface autoantibodies associated with cognitive deficits in cancer patients

J Neurol (2017) 264:1968–1977

Depression

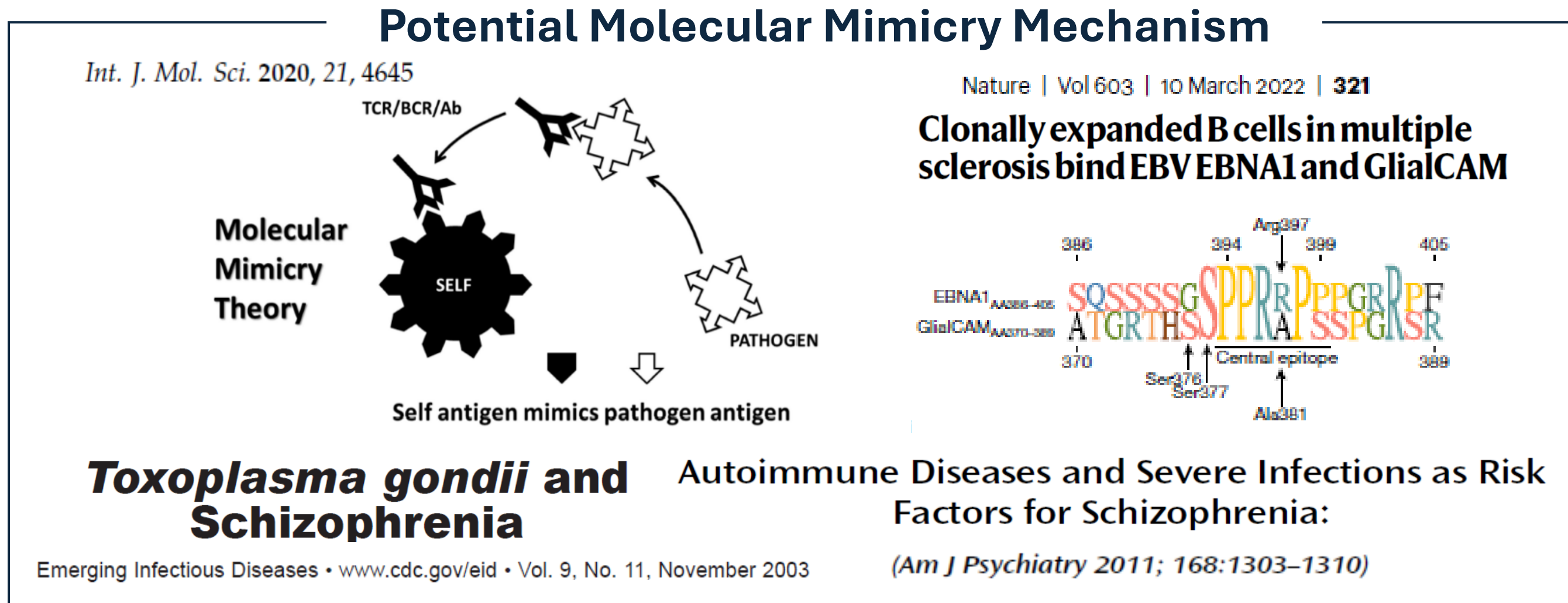
Anti-NMDA-receptor antibody in initial diagnosis of mood disorder (2019) 29, 1041–1050
European Neuropsychopharmacology

Molecular Mimicry mechanism may play in anti-NMDAR autoantibody generation

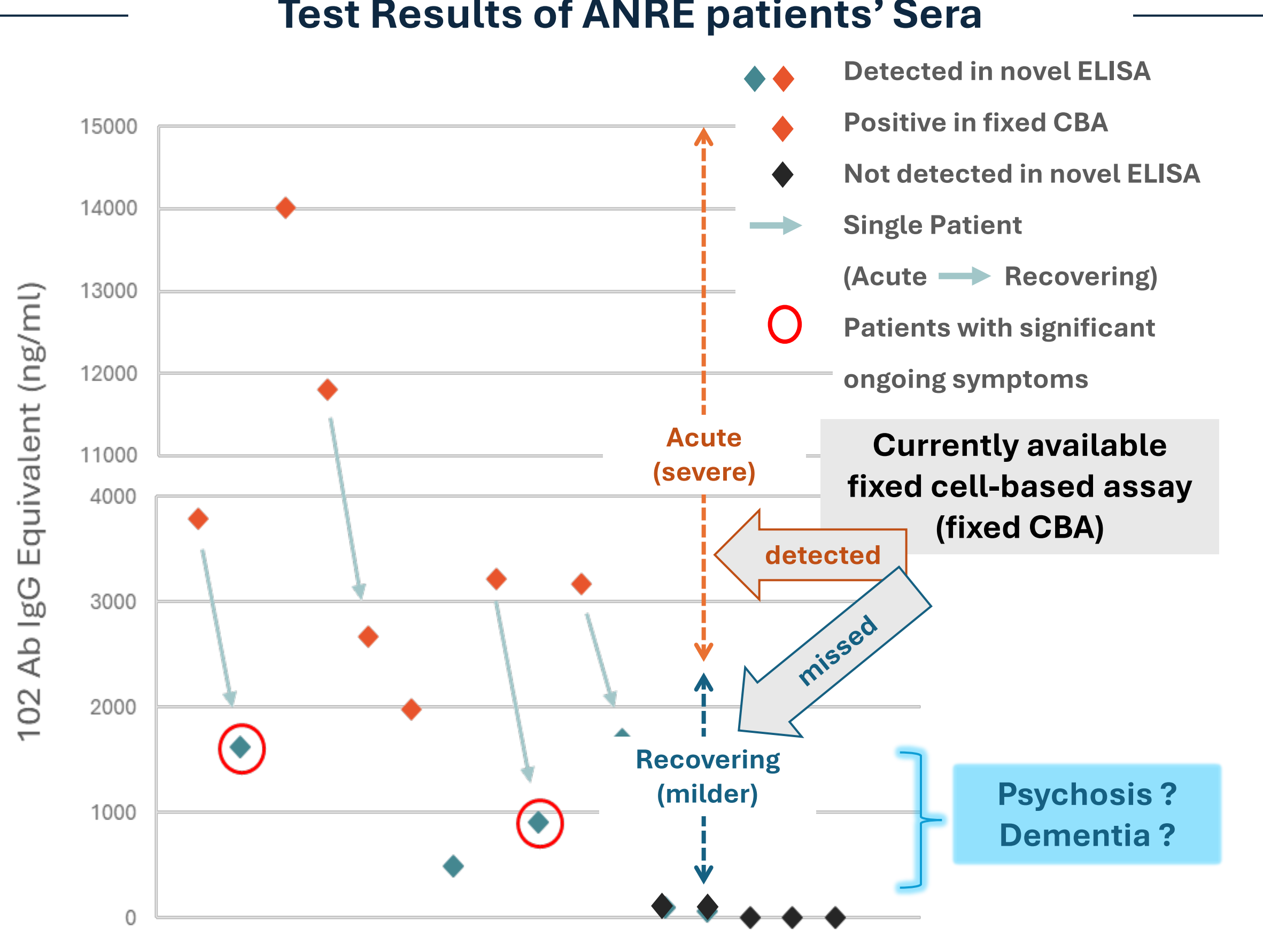
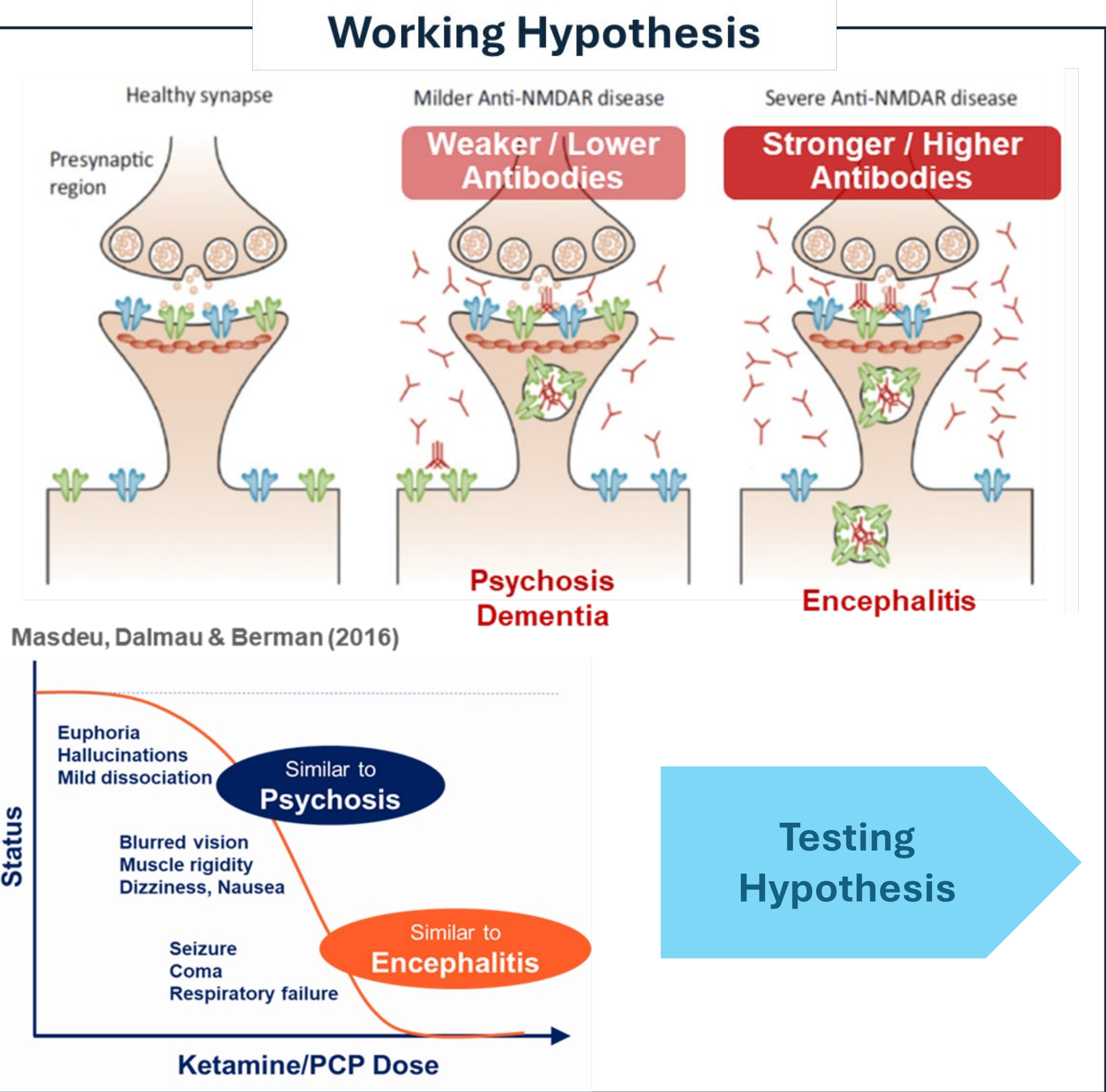
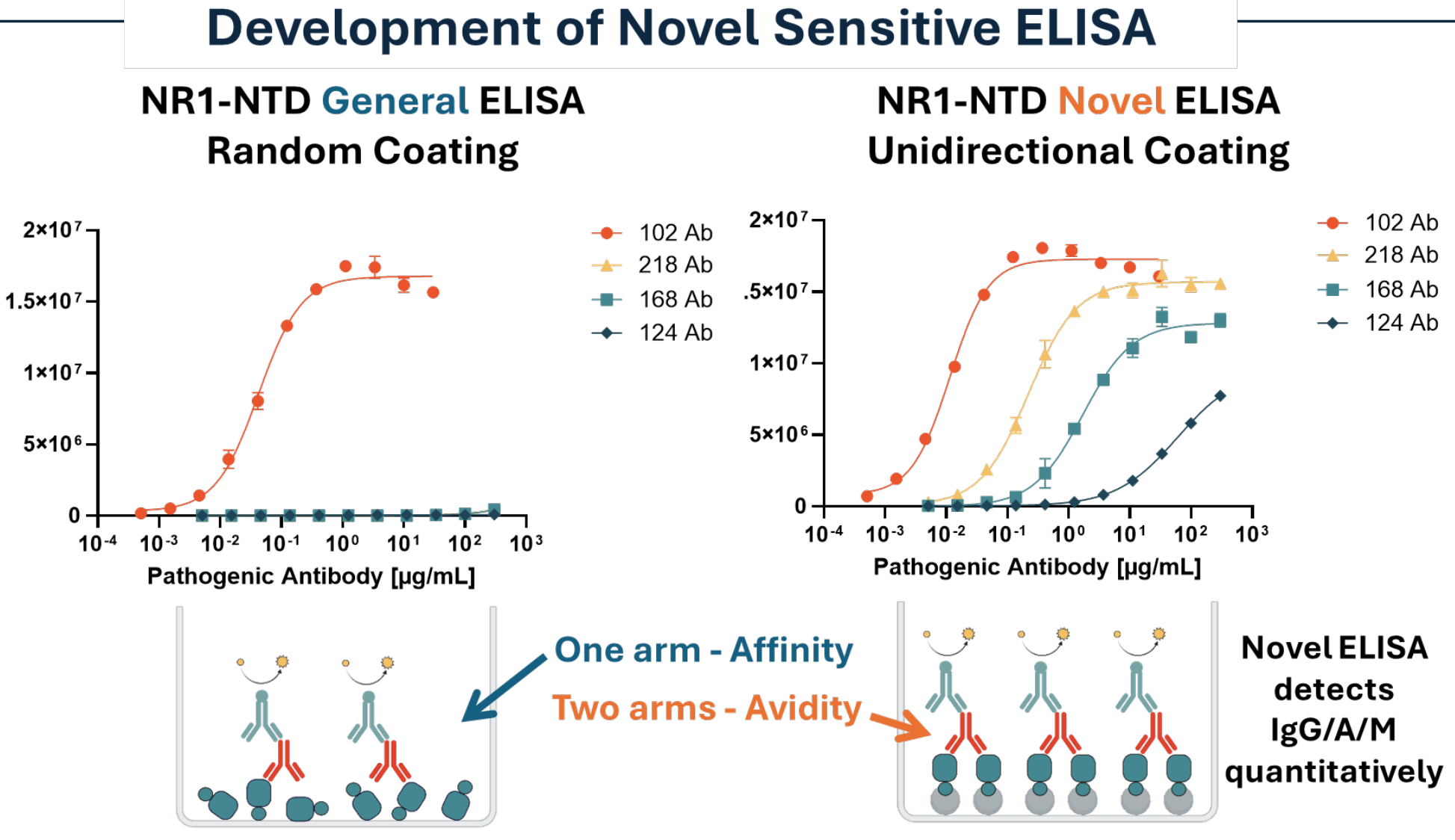


LQNRKLV is shared with Toxoplasma and bacteria proteins

Organism	Genus	Protein
Parasite	Toxoplasma	internal kinesin motor domain protein
	Campylobacter	tetratricopeptide repeat protein
	Enterococcus	DNA primase
	Peptoniphilus	hemolysin
	Paenacaligenes	LysR family transcriptional regulator
	Pseudomonas	2,5-dihydrogluconate reductase DkgB
	Burkholderia	Aldehyde reductase
	Chromobacterium	2,5-dihydrogluconate reductase DkgB
	Acinetobacter	LysR family transcriptional regulator
	Paenibacillus	Gfo/lsh/MocA family oxidoreductase
	Escherichia	2,5-dihydrogluconate reductase DkgB
	Nocardia	Hypothetical protein



A Novel ELISA to detect anti-NMDA receptor IgG, IgA, and IgM autoantibodies in blood samples from neuropsychiatric and neurologic patients



Disease category	NCNP (Japan)	Dr. Leweke (Germany)	Total
Healthy Control (HC)	200 (Young 100 - Old 100)	117	317
Bipolar Disorder (BPD)	100	51	151
Major Depression (MDD)	100	81	181
Schizophrenia (SCZ)	100	348	448
Alzheimer's Disease (AD)	100	-	100
Mild Cognitive Impairment (MCI)	100	-	100
Dementia other (DEM)	100	-	100
Epilepsy (EPL)	100	-	100
Parkinson's Disease (PD)	100	-	100
Autism (ASD)	20	-	20
Total	1020	597	1617

CONCLUSIONS

- While IgG anti-GluN1 autoantibodies are established mediators of ANRE, our data reveal that IgA and IgM autoantibodies binding to GluN1-NTD are also present in diverse neuropsychiatric conditions and can potentially induce NMDAR internalization.
- IgA is primarily produced in mucosal tissues, where it plays a critical role in defending against pathogens. However, recent discoveries of gut-educated, IgA-producing plasma cells in the dura mater, along with newly identified dura-brain connections through arachnoid cuff exit (ACE) points and perivascular spaces, suggest that IgA autoantibodies may have a pathogenic role, potentially triggered by molecular mimicry involving microbial antigens such as gut bacteria.
- Our novel ELISA provides a robust platform for detecting low-affinity or low-abundance autoantibodies and will facilitate future research into the pathogenic roles of not only IgG but also IgA and IgM NMDAR autoantibodies in neuropsychiatric disorders, and their potential as therapeutic targets.

Treatment Opportunity (ART5803)

