



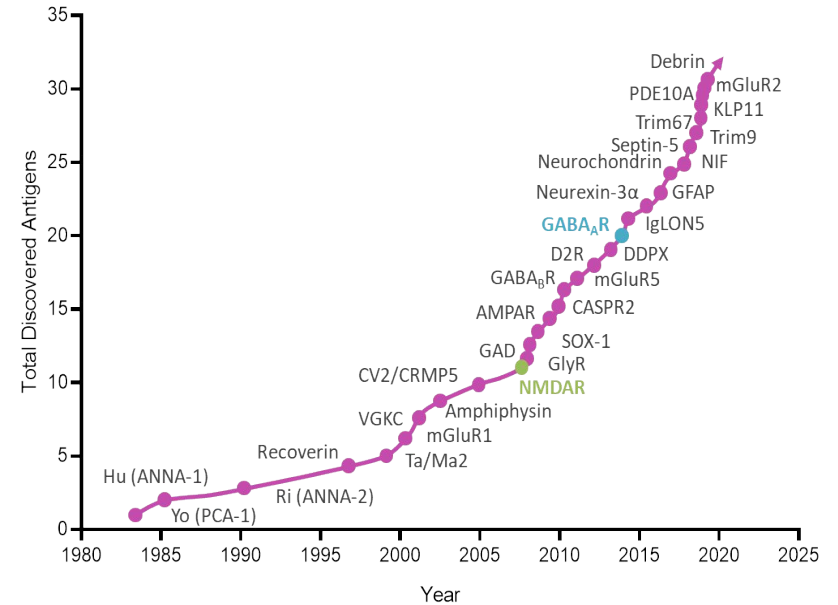
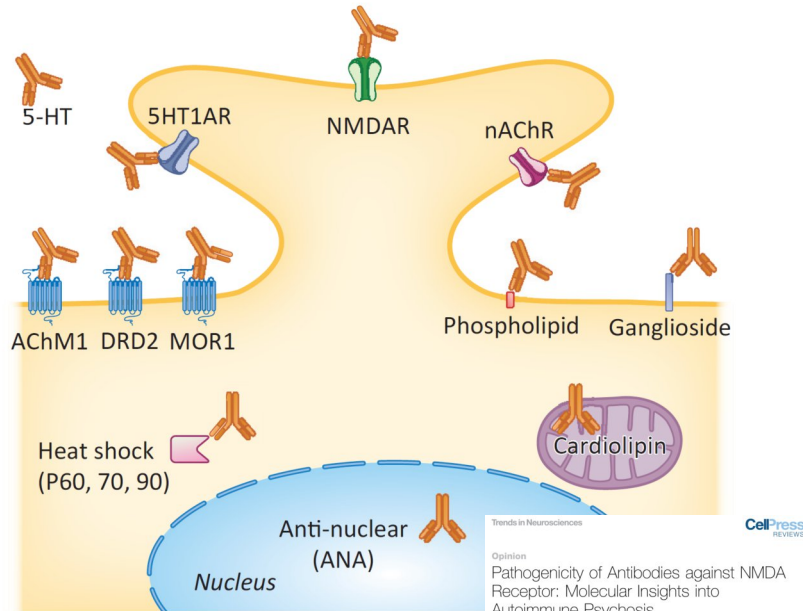
WP2 ImmunoPsy Project

Autoimmunity in psychosis

L. Groc (CNRS, Bordeaux) & U. Maskos (Pasteur, Paris)

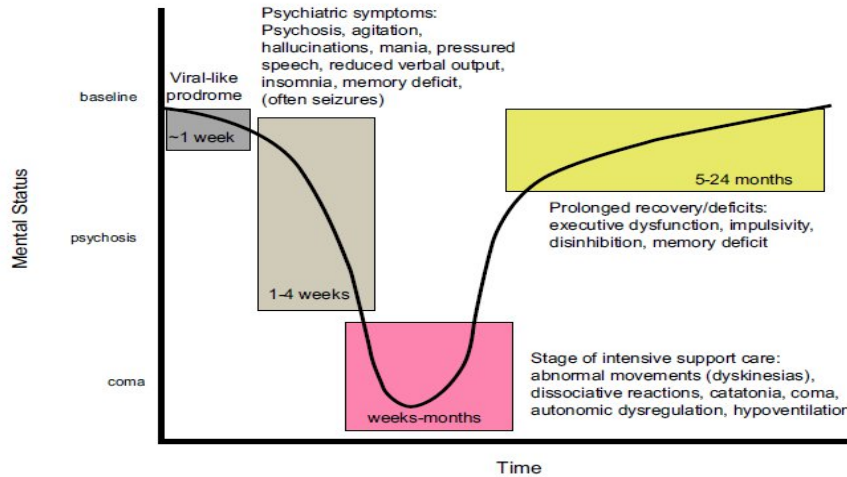
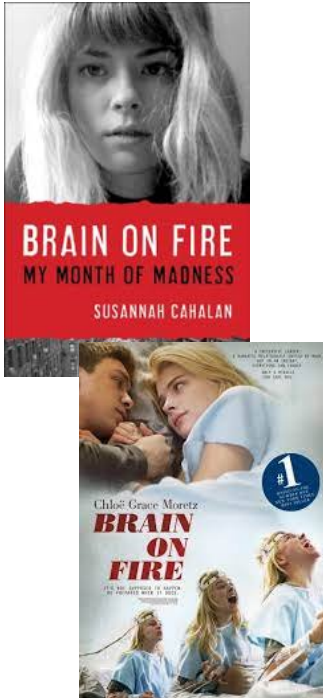
Autoantibodies directed against neurotransmitters in psychiatry

Selection of autoantibodies detected in patients diagnosed with schizophrenia



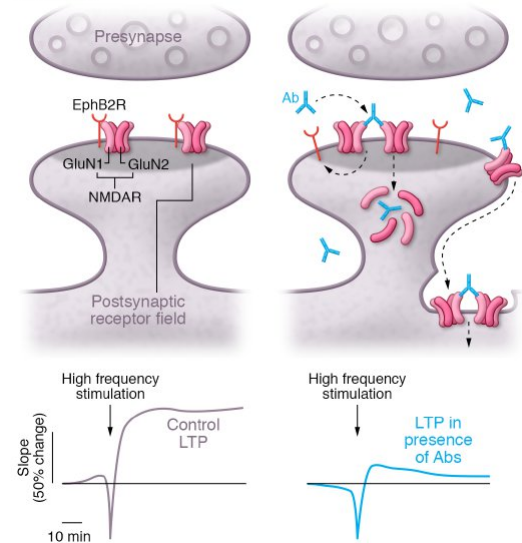
Geis et al., *JCI*, 2019

Case of the autoantibodies directed against NMDA receptor in encephalitis

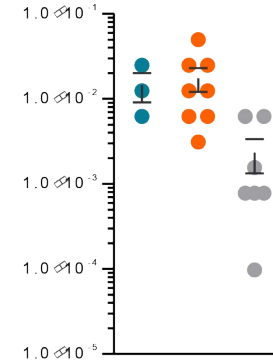
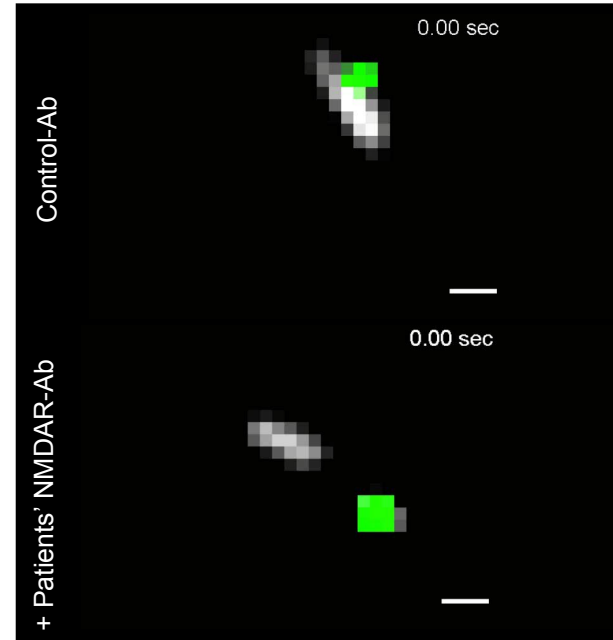
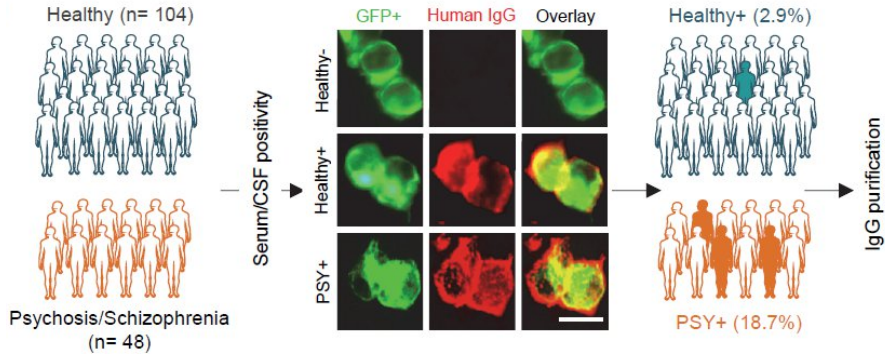


Dalmau et al., *Lancet Neurol.*, 2008

A NMDAR



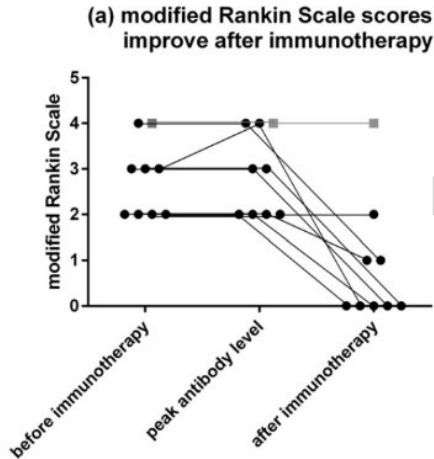
NMDAR-AAb detection in patients diagnosed with schizophrenia



Jezequel et al., *Nature Commun.*, 2017

Clinical relevance: ongoing clinical trials (UK & France)

Immunotherapy for patients with acute psychosis and serum N-Methyl D-Aspartate receptor (NMDAR) antibodies: A description of a treated case series



Zandi et al 2014

Open Access
Trials

STUDY PROTOCOL

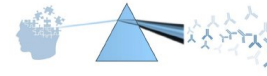
Intravenous immunoglobulin and rituximab versus placebo treatment of antibody-associated psychosis: study protocol of a randomised phase IIa double-blinded placebo-controlled trial (SINAPPS2)

Delphine Bouchet¹, Sarah-Anne Vicenz¹, Peter B. Jones¹, Michael David G. Owen^{2,3,4}, Louise H.J. Culverio^{1,5}, Rebecca Pollard¹, Sally-Anne Vicenz¹, Mo Shemabli¹, Iona Camit¹, Francis Dowling¹, Thomas Kabut¹, Thomas S. E. Barnes¹, Anne Lingford Hughes¹, Alison A. Housheer¹, Timothy Harrower¹, Camilla Buckley¹ and Richard Clark^{1*}



TiM-DePiS

Thérapeutique Immuno-Modulatrice après
DePiSTage spécifique devant des troubles
psychiatriques

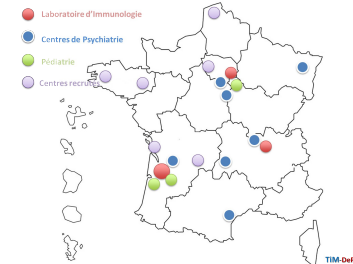
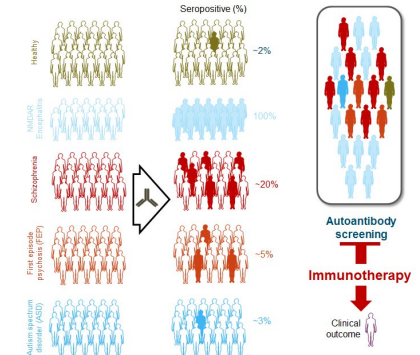


Guide de l'étude
à l'usage
des praticiens

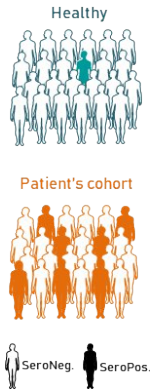
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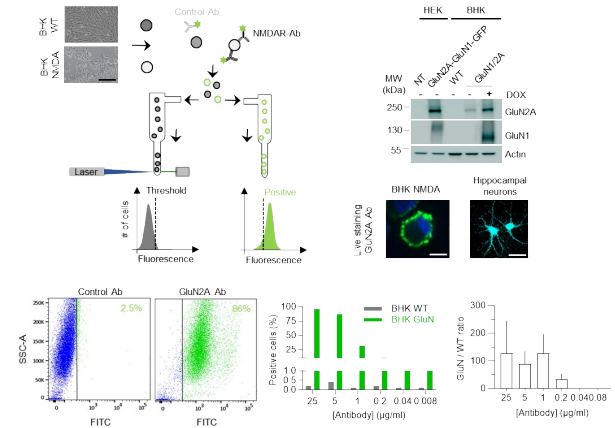
FrenchMinds WP1 Screening for AAbs in the cohort



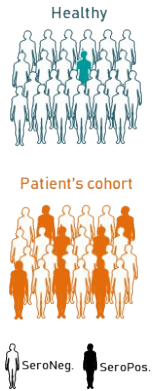
Circulating
autoantibody (AAb)
screening



NEW Detection Method Detection of Autoantibody against NMDAR by Cytometry (DANC)



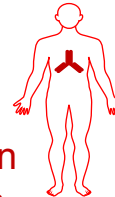
FrenchMinds WP1 Screening for AAbs in the cohort



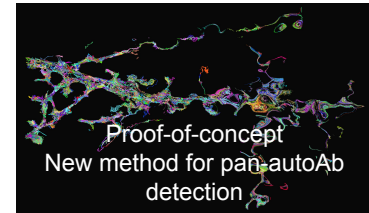
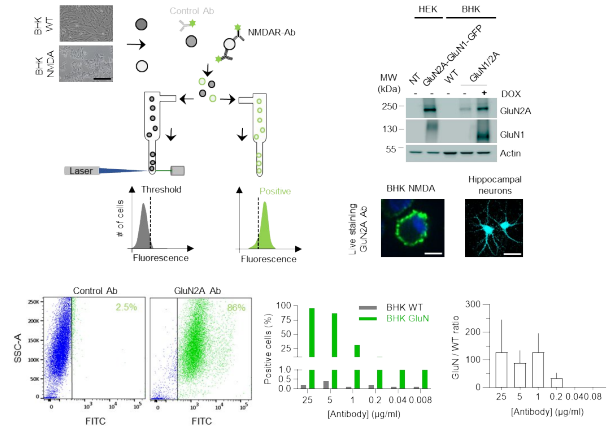
Circulating autoantibody (AAb) screening



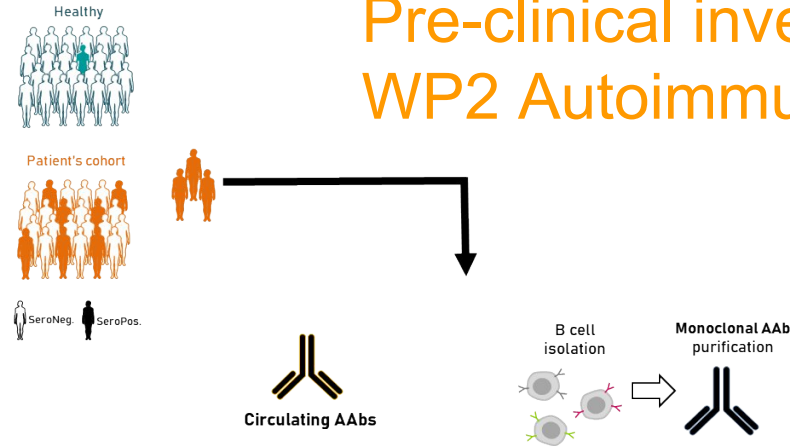
Urgent need to screen pathogenic pan-AAbs



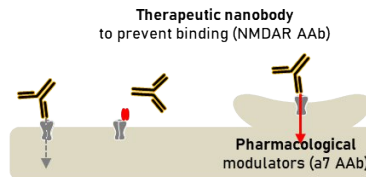
NEW Detection Method Detection of Autoantibody against NMDAR by Cytometry (DANC)



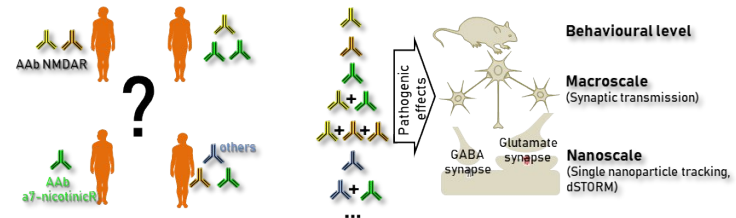
Pre-clinical investigation WP2 Autoimmunity Project



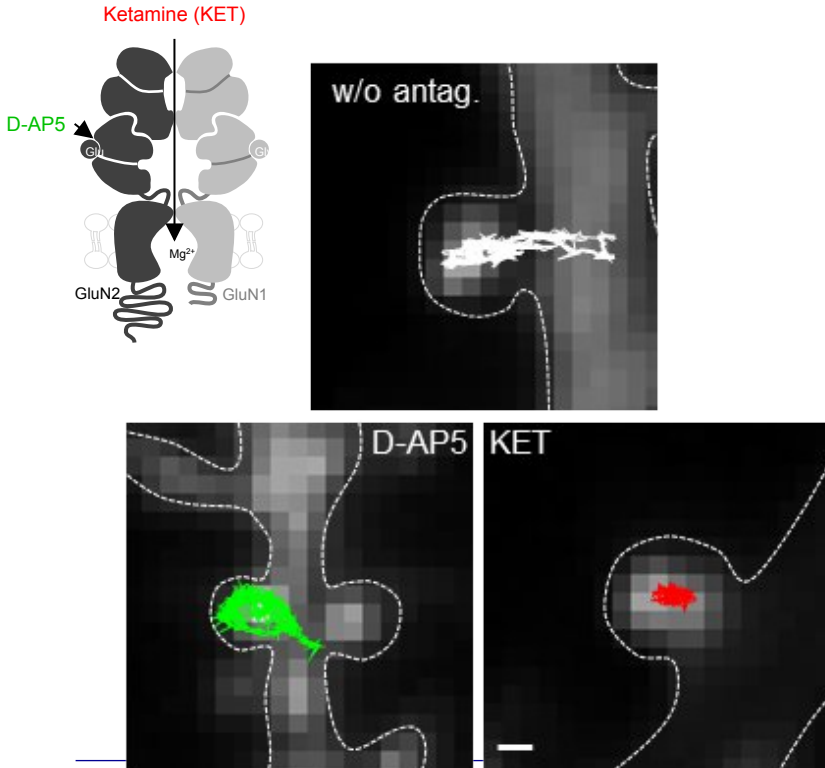
Neutralizing circulating AAb pathogeny with new probes



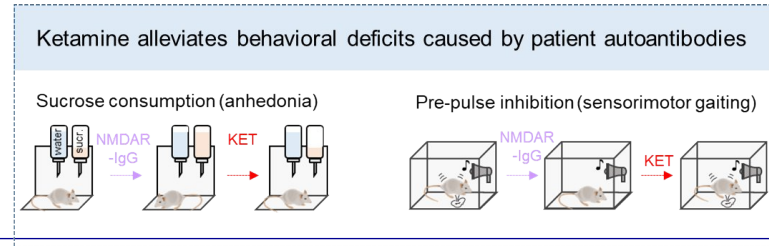
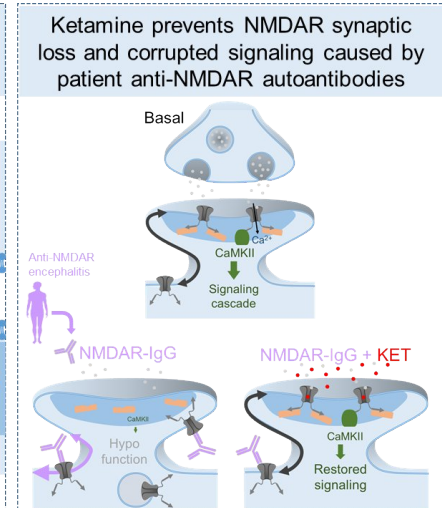
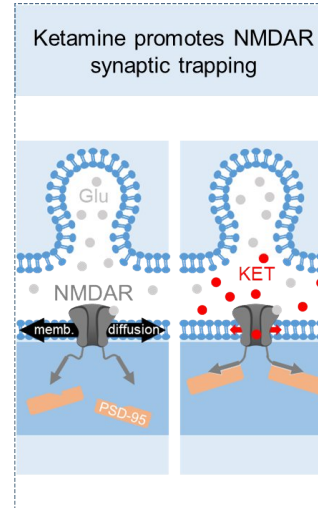
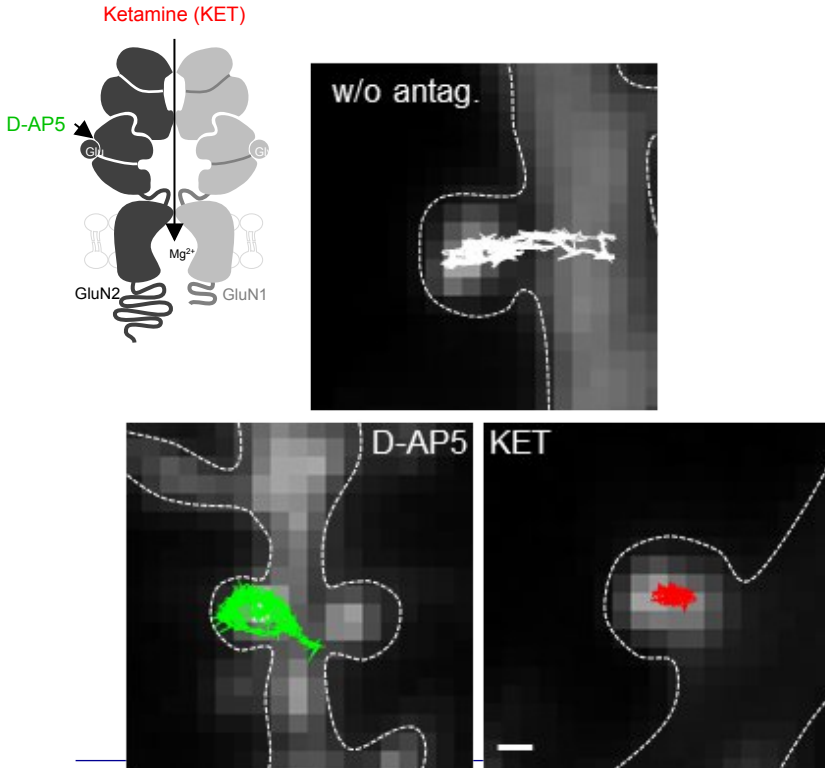
Characterization of AAb clones: *Pathogenic combination of AAb clones?*

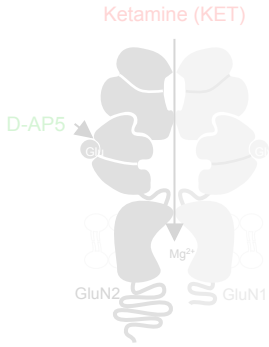


Can we use existing drugs to prevent AAb-mediated dysfunction?

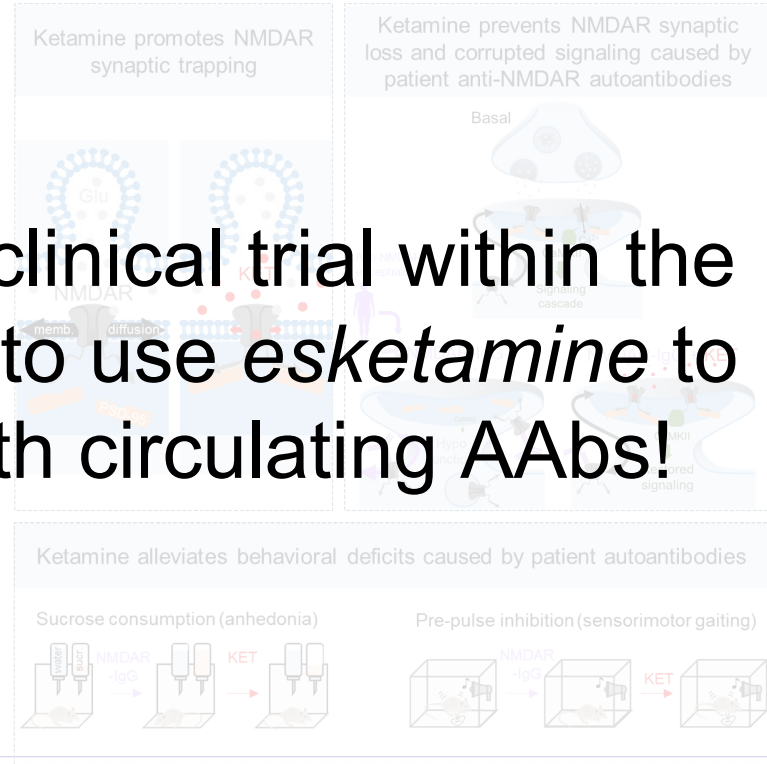


Can we use existing drugs to prevent AAb-mediated dysfunction?

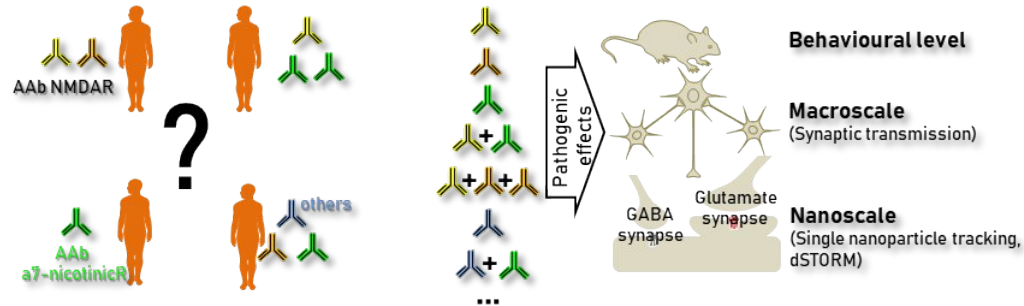




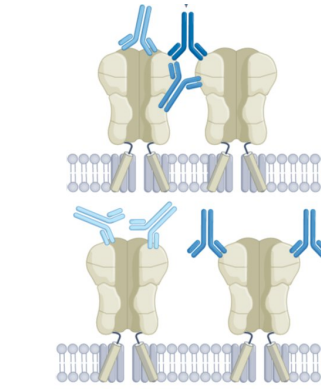
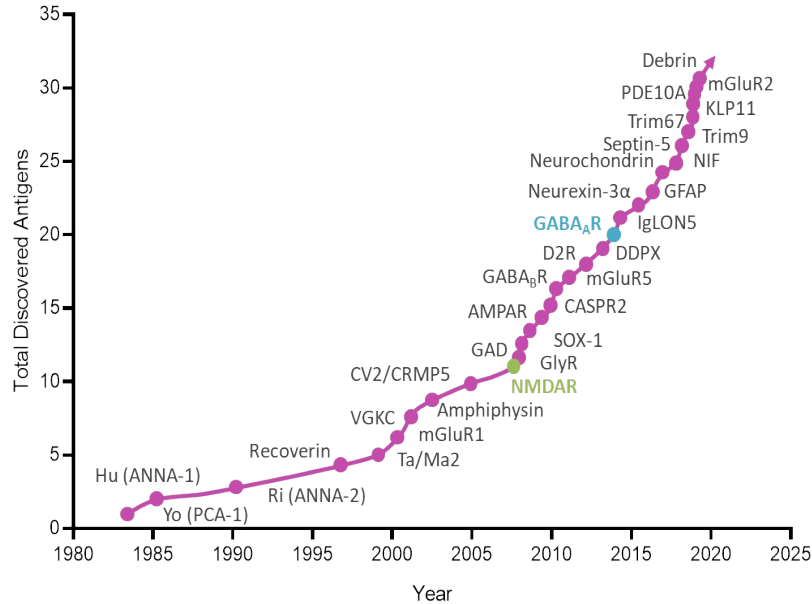
Opportunity for a clinical trial within the PEPR framework to use *esketamine* to treat patients with circulating AAbs!



Characterization of AAb clones: *Pathogenic combination of AAb clones?*



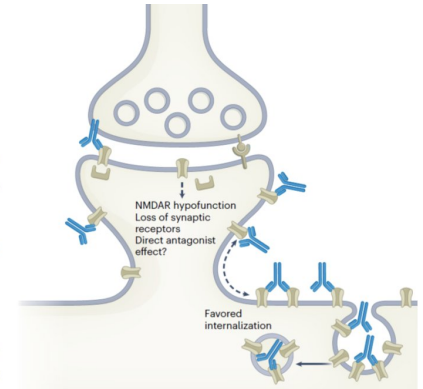
Clonal diversity: a key challenge



nature structural & molecular biology

Article
<https://doi.org/10.1038/s41594-024-01386-4>
Structural and functional mechanisms of anti-NMDAR autoimmune encephalitis

Received: 24 October 2023
 Accepted: 7 August 2024
 Kevlin Michalak¹, Taha Abulafia¹, Sam Kleemann¹, Lars Schendel¹, Ricardo Gómez¹, Mariko Simorowski¹, Francesca Vallasek¹, Harald Prineas¹, Manfred Meckmann¹, Christian Giese¹ & Hiro Funakawa¹✉



nature structural & molecular biology

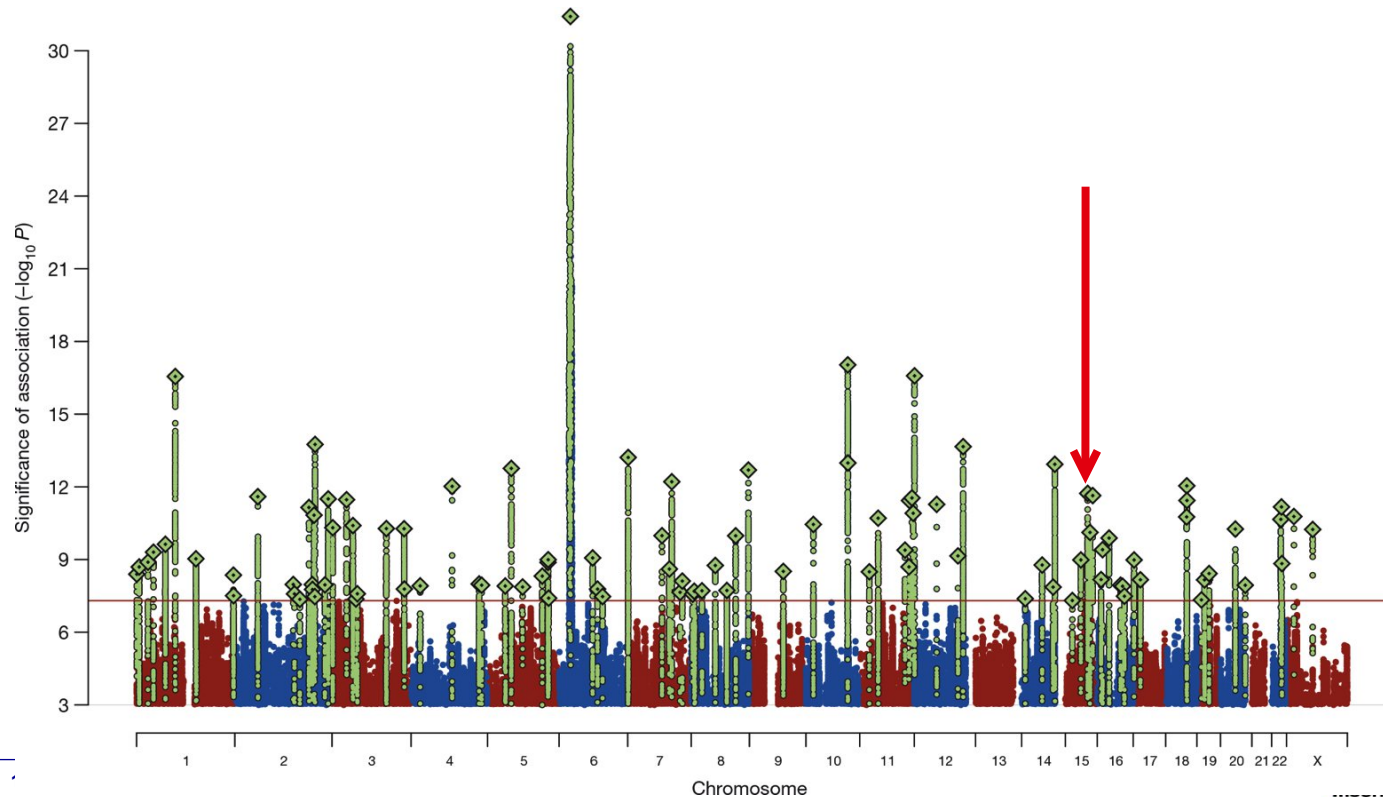
Article
<https://doi.org/10.1038/s41594-024-01387-3>
Structural basis for antibody-mediated NMDA receptor clustering and endocytosis in autoimmune encephalitis

Received: 24 October 2023
 Accepted: 7 August 2024
 Published online: 01 September 2024
 Han Wang¹, Chun Xie¹, Bo Dong¹, Jinglin Ding¹, Xu Li¹, Zhenqiang Kang¹, Mengmeng Jin¹, Jie He¹, Genwei Wang¹, Han Wu¹, Jialan Zhang¹, Qingqing Zhou¹, Sheng Chen¹, Xiangchen Chen¹, Yi Fan Yuan¹ & Shijia Zhu¹✉

1. Intérêt du récepteur cholinergique

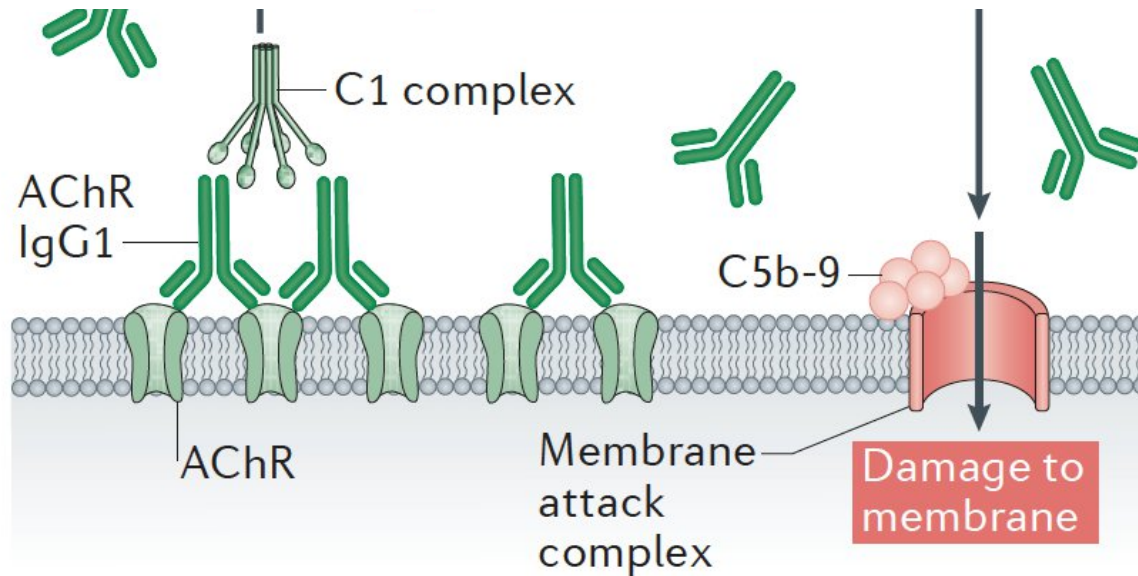


Génétique humaine: GWAS schizophrénie

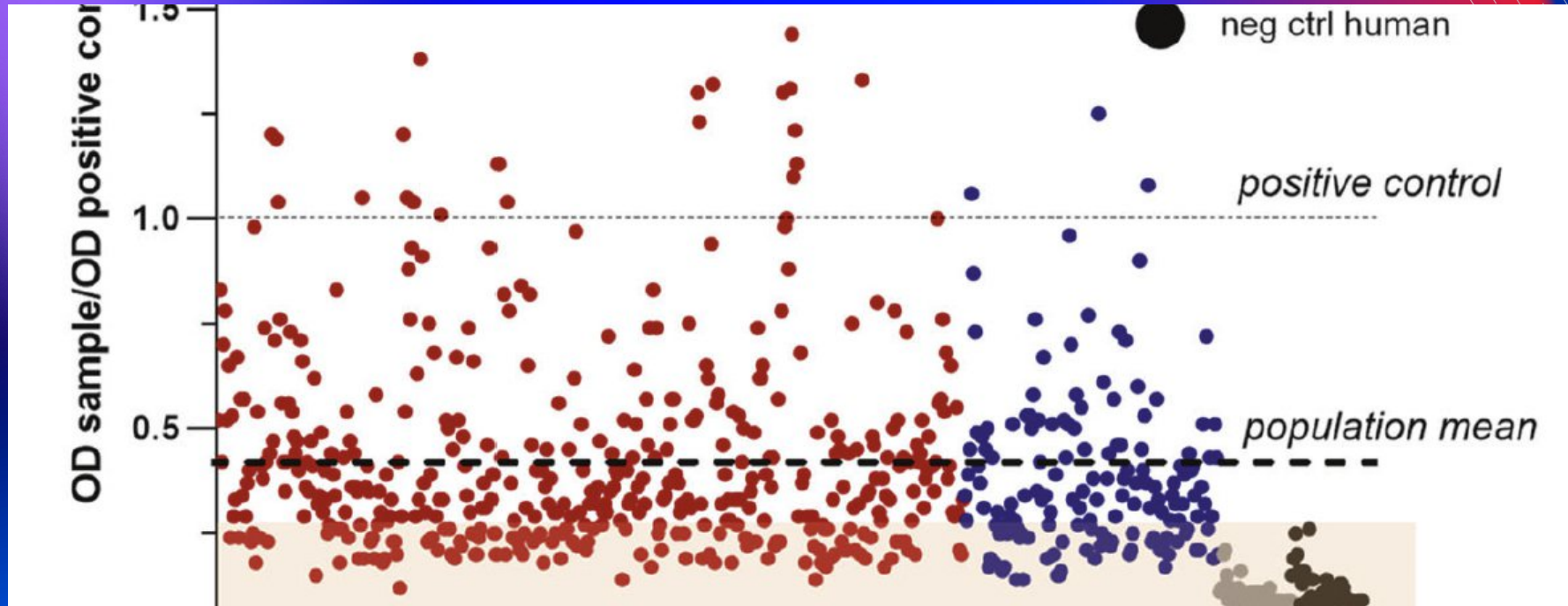


AUTOANTIBODIES TO GANGLIONIC ACETYLCHOLINE RECEPTORS IN AUTOIMMUNE AUTONOMIC NEUROPATHIES

STEVEN VERNINO, M.D., PH.D., PHILLIP A. LOW, M.D., ROBERT D. FEALEY, M.D., JOHN D. STEWART, M.B., B.S.,
GIANRICO FARRUGIA, M.D., AND VANDA A. LENNON, M.D., PH.D.

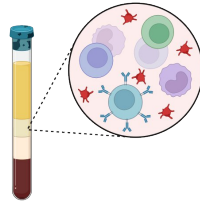


2. Analyse des auto-anticorps

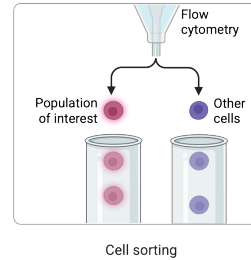


Culture des PBMC

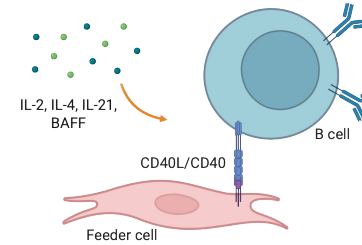
- ① PBMC from psychotic patients



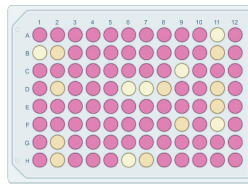
- ② Sort PBMC positive selected for CD19/CD27/nAChRα7



- ③ Co-culture B-cells with feeders cells for 25 days to induce B cell proliferation and maturation

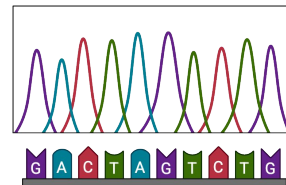


- ④ Cultured B cells are positive selected against nAChRα7 ECD.

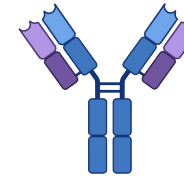


Screening

- ⑤ Sequencing of antibodies



- ⑥ Purification and recombinant expression of α7 antibodies

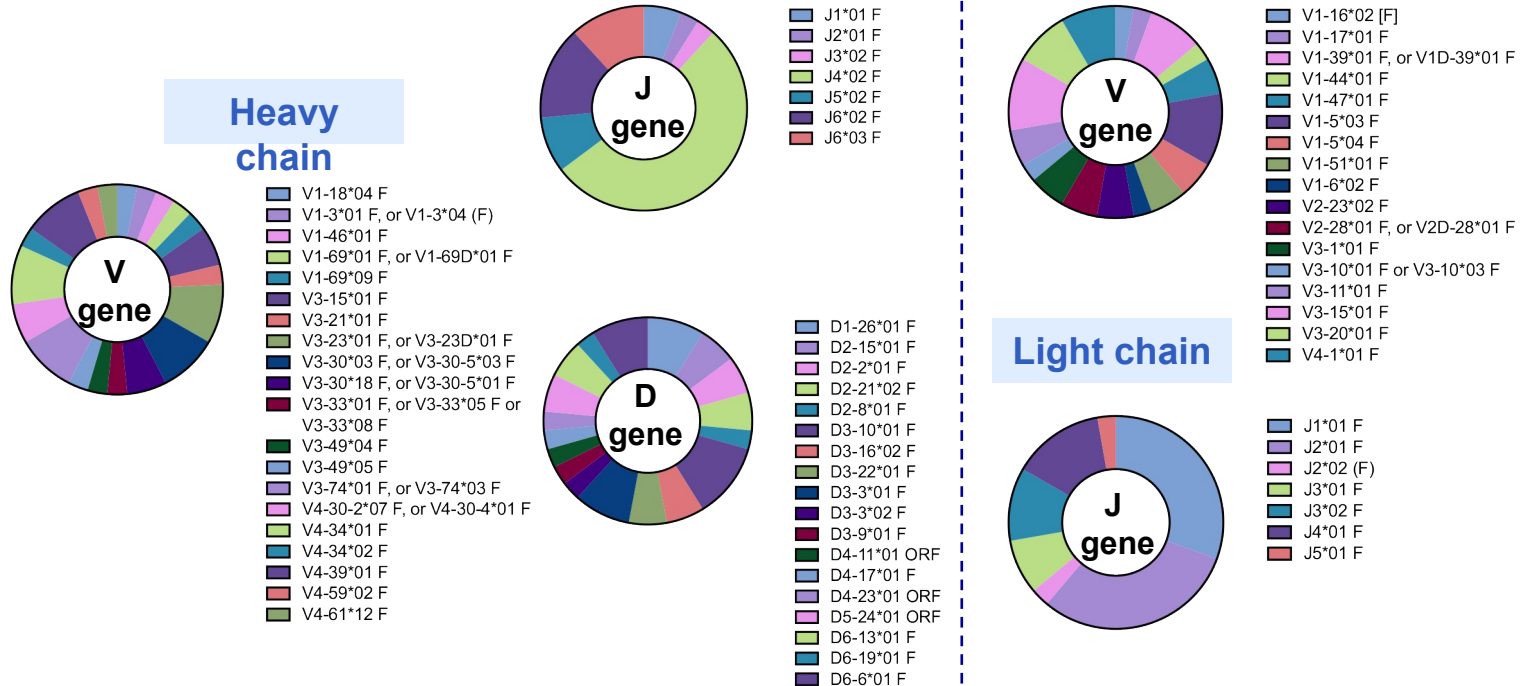


IgG/IgM antibodies

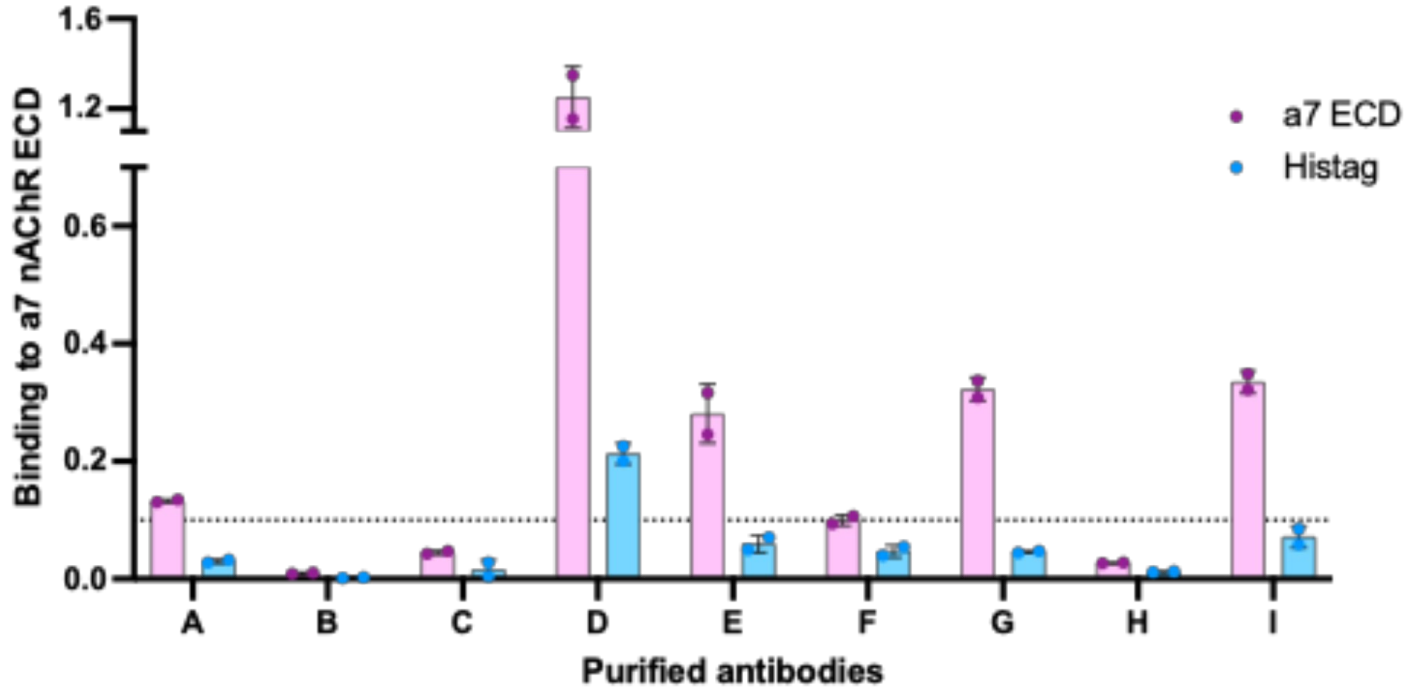
Les clonages effectués

Sort	Date	Cohort	Sample	Cells in vial	Total cells sorted	Clones with a7 ECD reactivity
A	18/05/2024	I-GIVE	IG-001-681 IG-001-622	$4 \cdot 10^5$ $1 \cdot 10^6$	96 460	- 1
D	22/01/2025	I-GIVE	IG-001-137	$4,73 \cdot 10^6$	490	19
E	13/02/2025	I-GIVE	IG-001-681	$2,71 \cdot 10^6$	249	11
F	13/02/2025	I-GIVE	IG-001-325	$4,43 \cdot 10^6$	6	1
G	07/04/2025	I-GIVE	IG-001-331	$9,70 \cdot 10^6$	288	1
H	07/04/2025	I-GIVE	IG-001-628	$3,65 \cdot 10^6$	204	2

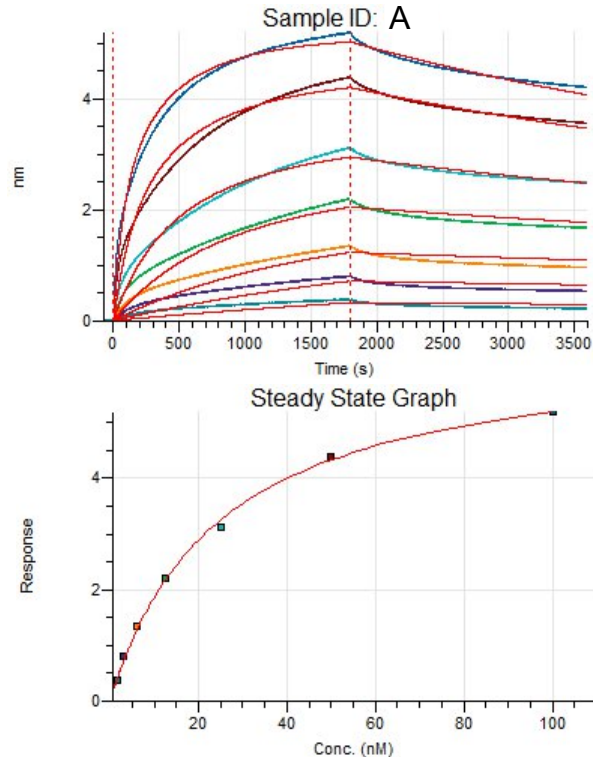
Séquençage des auto-anticorps (AAc)



Caractérisation biochimique



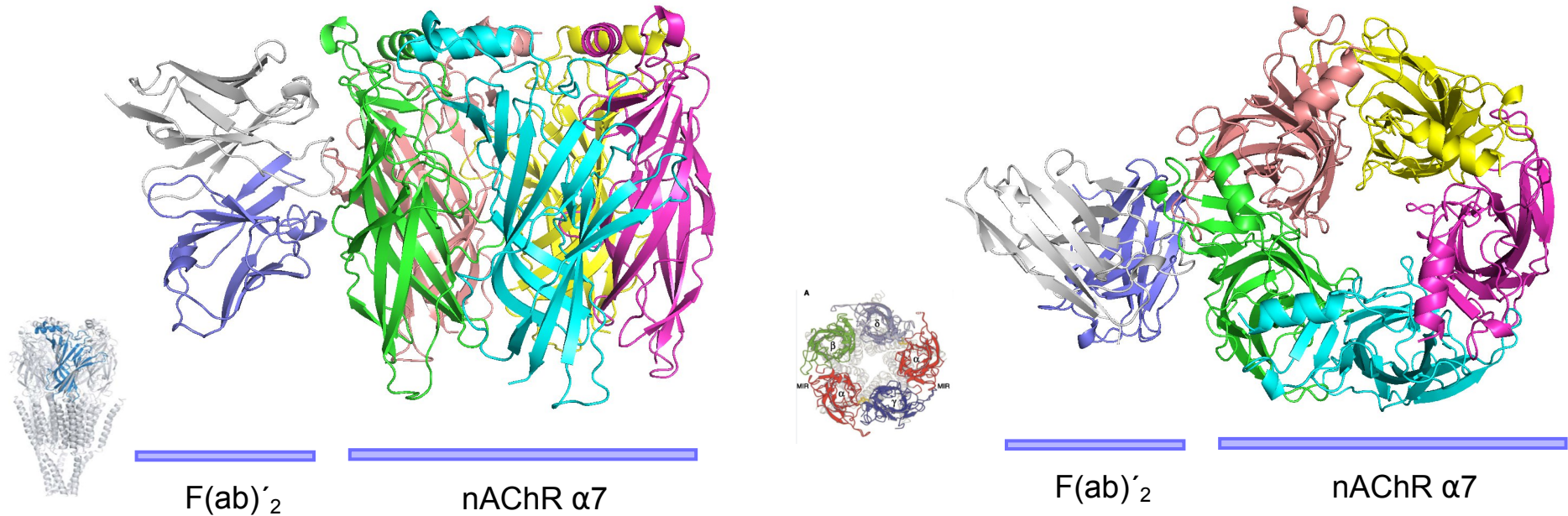
Mesures de l'affinité des AAc



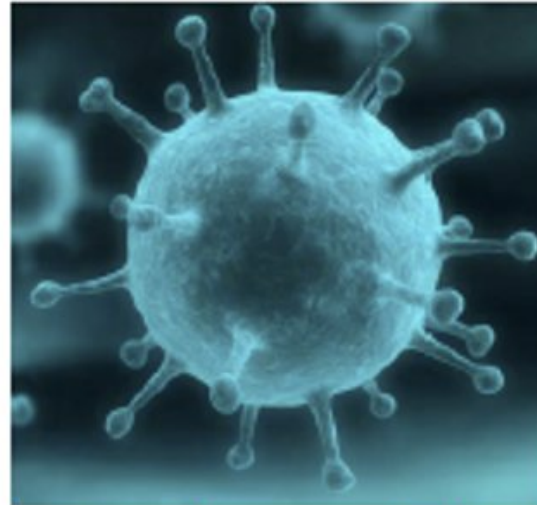
	Steady State
	Association/Dissociation
Sample	alpha 7 ECD
A	2.23E-08
B	6.55E-08
C	5.98E-08
D	1.80E-07
E	7.35E-08
F	8.27E-08
G	7.52E-08

Modélisation du site de liaison

Docking alpha 7 nAChR vs Antibody A F(ab)₂



3. Prospectives: la genèse des AAb



Virus Influenza A (H3N2)

Prospectives: les AAb du LCR

HIGH
LIGHT

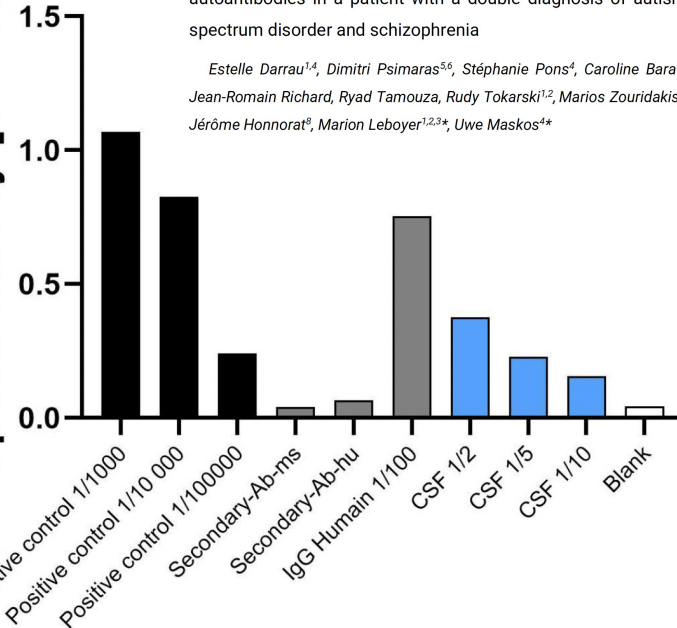
α7-Acetylcholine receptor antibodies in two patients with Rasmussen encephalitis

Abstract—Rasmussen encephalitis (RE) sera were screened for antibodies to human α7 nicotinic acetylcholine receptors (nAChRs) using electrophysiology, calcium imaging, and ligand binding assays. Sera from two of nine patients with RE blocked ACh-induced currents through α7 nAChRs and the AC induced rise in intracellular free calcium ($[Ca^{2+}]_i$) and inhibited ^{125}I -bungarotoxin binding in cells expressing α7 nAChRs. Thus, the α7 nAChR is potential target for pathogenic antibodies in patients with RE.

NEUROLOGY 2005;65:1802–1804

R. Watson, DPhil; J.E.C. Jepson, BSc; I. Bermudez, PhD; S. Alexander, BSc; Y. Hart, MD, FRCP; K. McKnight, MRCP; A. Roubertie, MD; F. Fecto; J. Valmier, MD, PhD; D.B. Sattelle, ScD; D. Beeson, PhD; A. Vincent, FRCPath; and B. Lang, PhD

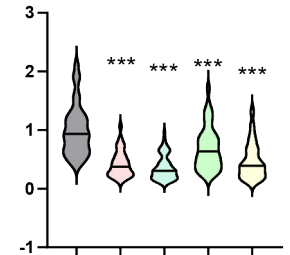
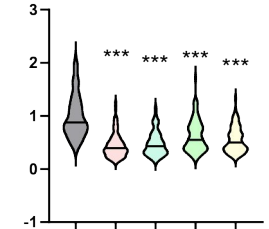
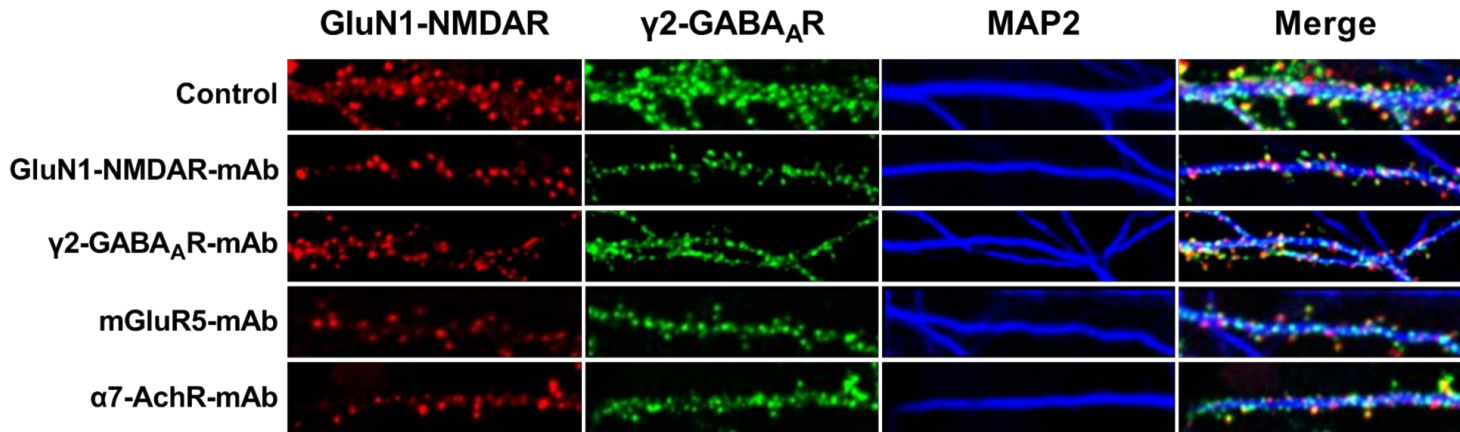
Optical density [490-415]



A case of anti-α7-nicotinic receptors and NMDA autoantibodies in a patient with a double diagnosis of autism spectrum disorder and schizophrenia

Estelle Darrau^{1,4}, Dimitri Psimaras^{5,6}, Stéphanie Pons⁴, Caroline Barau, Jean-Romain Richard, Ryad Tamouza, Rudy Tokarski^{1,2}, Marios Zouridakis⁷, Jérôme Honnorat⁸, Marion Leboyer^{1,2,3*}, Uwe Maskos^{4*}

Preliminary evidence: convergence of excitatory/inhibitory unbalance between different Aabs!



Conclusions (1/1.5 an après démarrage WP2 ImmunoPsy)

- ✓ Identification de molécules (cliniquement pertinentes) qui peuvent réduire les effets pathogéniques des AAcS. Test de Nouvelles molécules en cours.
- ✓ Identification d'effets moléculaires convergents entre différents AAcS
- ✓ Production d'AAcS monoclonaux nicotiniques. Pipeline en cours pour d'autres AAcS.

WP1 – FrenchMinds: nouvelle méthode de detection à haute sensibilité prête!