



Regulatory T Cells in Schizophrenia Patients with Positive Anti-Gliadin Antibody (AGA) Titers Correlate Negatively with AGA IgG Levels and with Negative Symptoms

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Background

- Immune dysfunction has increasingly been identified as a part of the pathogenic process in schizophrenia. there is an elevation of anti-gliadin.
- IgG antibodies (AGA-IgG) are associated with increased levels of TNF- α , IL-1, and kynurenine – all markers of pro-inflammation.
- Previously shown that patients with schizophrenia have an elevated antibody titer to Gliadin (Anti-Gliadin Antibody).
- Gliadin (protein found in gluten) is highly immunogenic and contributes to a “leaky gut”.
- Natural Regulatory T cells (nTregs), defined in this study as CD3+CD4+CD25+Foxp3+ are immunosuppressive T cells that can sequester pro-inflammatory immune cell growth factors, directly inhibit other immune cells, and secrete anti-inflammatory cytokines (i.e. IL-10, IL-35, TGF- β).
- Previously shown that nTregs are increased and correlate with decreased negative symptoms in schizophrenia.
- AIM: To evaluate this relationship within the subgroup of schizophrenia patients known to have an immune response to AGA.

Study Methods and Demographics

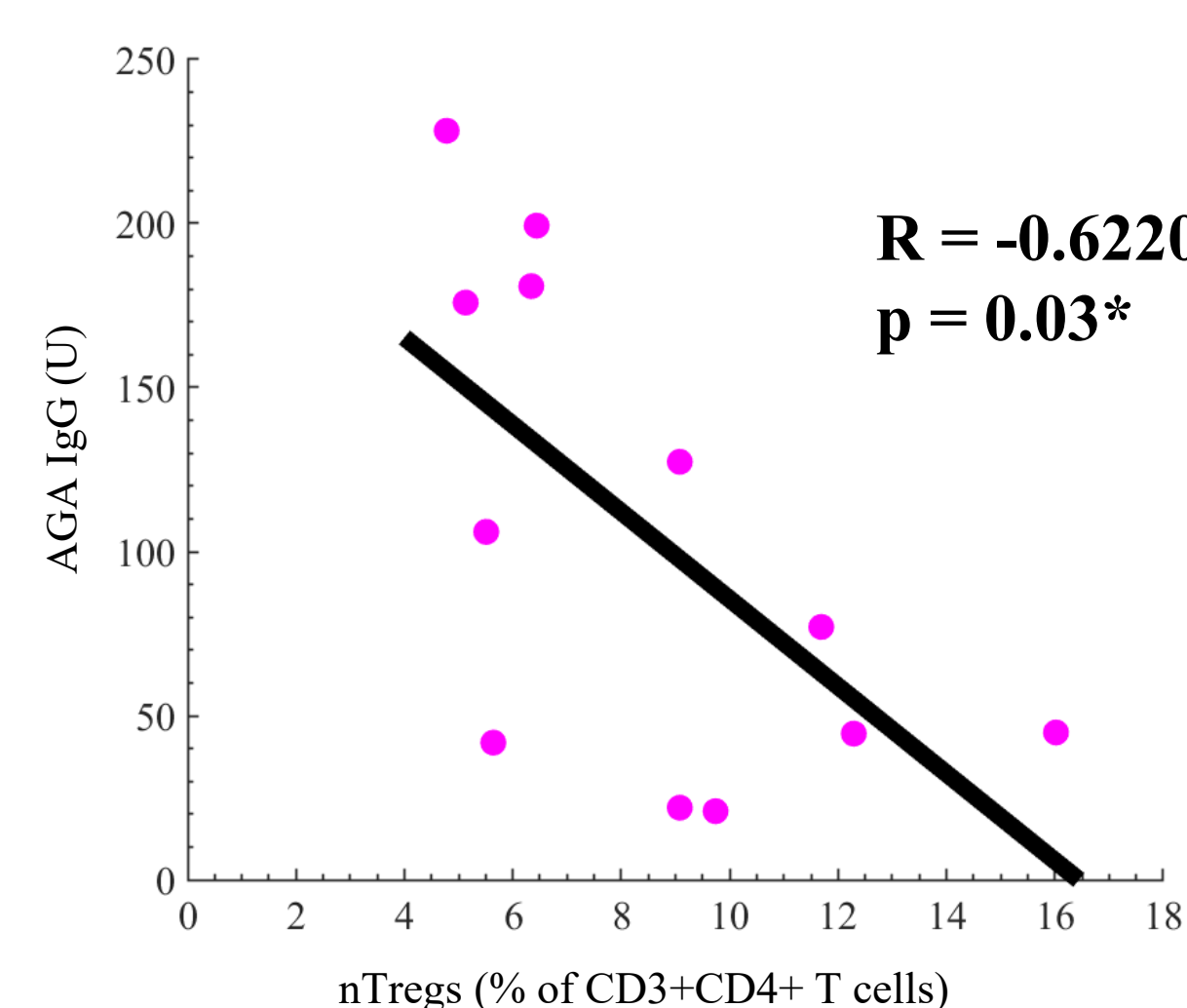
- A cross-sectional study. In total, 17 Healthy Controls (HC) and 26 patients with a DSM-IV-TR or DSM-5 diagnosis of schizophrenia or a schizophrenia related disorder were ultimately included.
- We collected regulatory T cell measurements and AGA-IgG levels:
- Peripheral Blood mononuclear Cells were isolated from whole blood were stained with CD3 (T cell marker), CD4 (Helper T cell marker), CD8 (Killer T cell marker), CD25 (high affinity IL-2R), CD45RA (activation status) and Foxp3 (Treg master transcription factor) prior to flow cytometric analysis. For this study, we define nTregs (natural Tregs) as CD3+CD4+CD25+Foxp3+.
- AGA-IgG was measured using ELISA.
- Scale for the Assessment of Negative Symptoms (SANS) was used to evaluate negative psychiatric symptoms. We also looked at the alogia item of the SANS.
- Pearson’s correlation coefficients were utilized for correlations between mTregs and antibody levels and Spearman’s Rank Correlation utilized for correlations in non-normal distributions.
- Cutoff for positive AGA-IgG titer was set to greater than or equal to 20 U.

Group	Average Age	Sex
Healthy Control	38 \pm 12	8F, 9M
Schizophrenia	46 \pm 11	7F, 19M

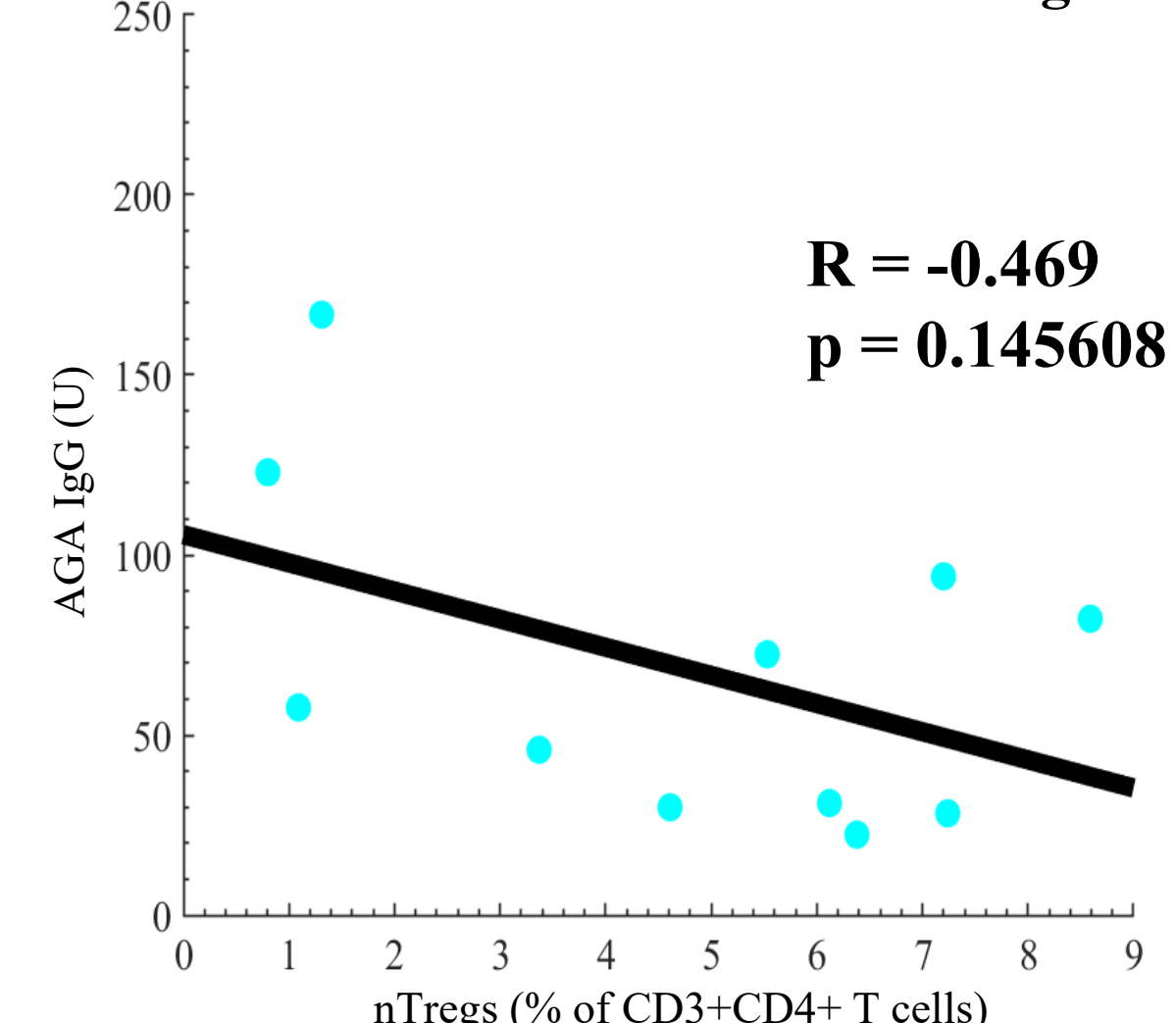
- Other clinical information collected:
- Height, weight, temperature, heart rate, blood pressure.
- PMHx, Smoking history, CBC, CMP - apart of brief evaluation of acute infection, in order to control for possible alternative sources of inflammation (i.e. infection) – part of exclusion criteria.

Higher nTreg (%) in Positive AGA IgG

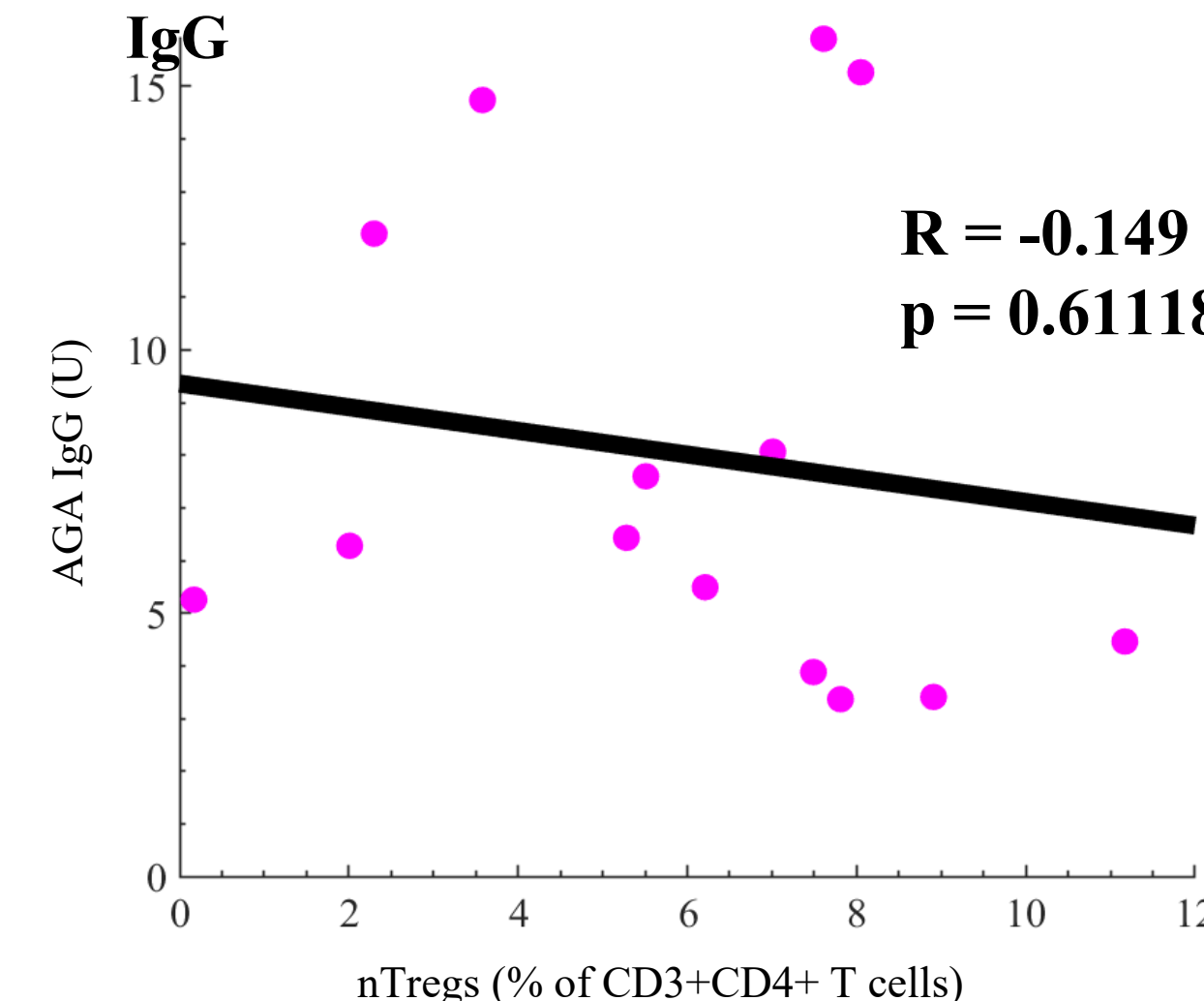
Schizophrenia Patients With Positive AGA IgG



HC With Positive AGA IgG



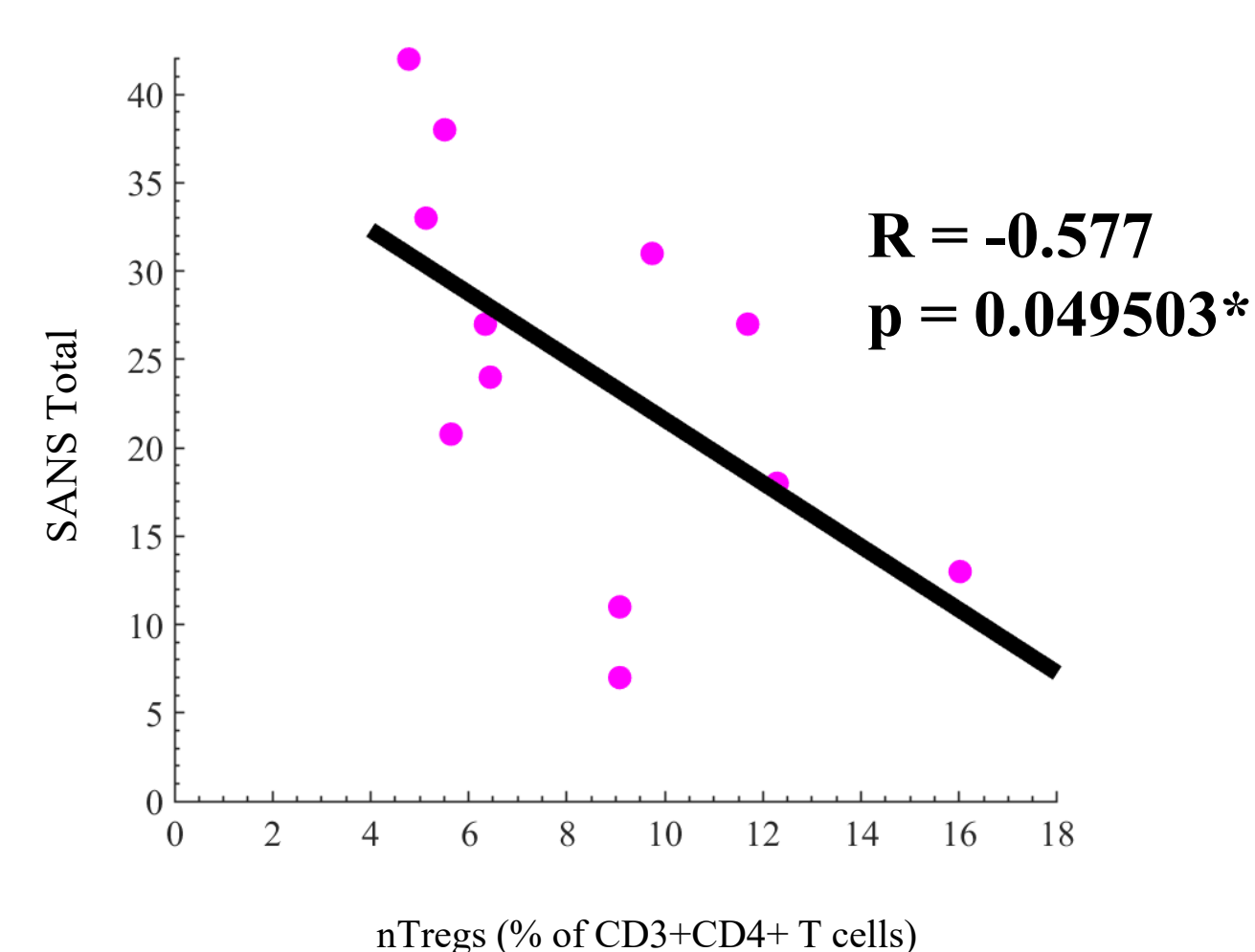
Schizophrenia Patients With Negative AGA IgG



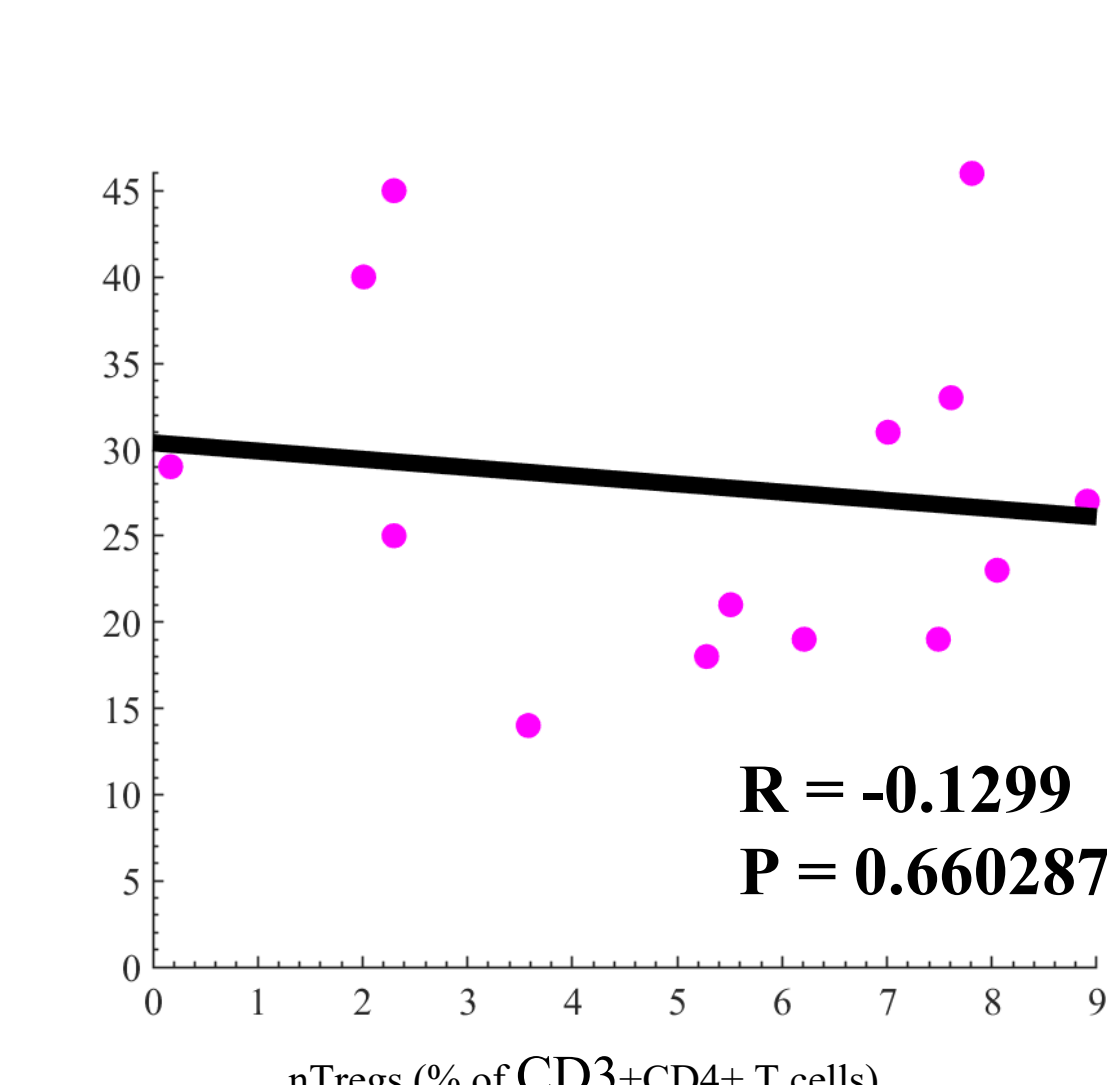
In schizophrenia patients with positive AGA-IgG titers, there is a negative correlation between nTregs (CD3+CD4+CD25+Foxp3+) and AGA-IgG levels which was not evident in HC with a positive titer (R = -0.62, p = 0.03* vs. R = -0.47, p = 0.15), nor in schizophrenia patients with a negative AGA-IgG titer (R = -0.15, p = 0.61).

Higher nTreg (%) Correlates with Less Total SANS

Schizophrenia Patients With Positive AGA IgG



Schizophrenia Patients With Negative AGA IgG



• Schizophrenia patients with positive AGA-IgG titer but not in schizophrenia patients with a negative AGA-IgG titer: there is a negative correlation between nTregs ((CD3+CD4+CD25+Foxp3+) and SANS Total (R = -0.58, p = 0.04* vs. R = -0.13, p = 0.66)

Higher Treg (%) Correlates with Less Alogia

Condition	Spearman Rank Correlation Coefficient	P value
Positive AGA IgG in patients with schizophrenia	rs = -0.63925	p = 0.02522*
Negative AGA IgG in patients with schizophrenia	rs = -0.37002	p = 0.19284 (NS)

- Patients with schizophrenia who have positive AGA IgG or negative IgG
- Positive AGA-IgG titer, but not schizophrenia patients with a negative AGA-IgG titer, had a negative correlation between nTregs (CD3+CD4+CD25+Foxp3+) and SANS Alogia (Spearman Rank's Correlation rs = -0.64, p = 0.03* vs. rs = -0.37, p = 0.19).

Other Data

- In healthy controls with negative (or equivocal) AGA-IgG titers (n=5), there is a statistically significant positive correlation between nTregs (%) and AGA-IgG levels.

Discussion

- First investigation into the role of Tregs in an AGA positive schizophrenia cohort. Tregs appear to be negatively correlated with AGA-IgG titers, SANS Total, and SANS Alogia. Notably, this correlation between nTregs, total AGA-IgG titer, and negative symptomology was not similarly present in the negative AGA group.
- This sample size is relatively small, these findings are certainly suggestive of potential protective roles of nTregs in this gluten-sensitive cohort of patients with schizophrenia.

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