Letter to the Editor: evidence of aberrant anti-Saccaromyces cerevisiae autoantibodies in human autoimmune diseases and experimental background of their ability to cross-react.

Dear Sir,

The article on the possible immunomodulatory effects of dietary yeasts on the central nervous system, notably the experimental autoimmune encephalomyelitis (EAE) mouse model, greatly attracted our attention [1]. This final anti-inflammatory outcome seems to be in contrast to several experimental models and clinical evidence that our group was first to review [2].

In fact, mice were shown to develop a significant reduction of pro-inflammatory cytokines such as IL17 and IFNγ only in response to *C. kefir* compared to controls. Additionally, the level of pro-regulatory IL10 (just under 20 ng/mL) was also as low as in unexposed mice. Exposure to other yeasts within the same experiment did not provide similar results and neither *C. kefir* nor *S. cerevisiae* could ameliorate TDI-induced autoimmune dermatitis in mice [1].

On the other hand, it is held that even commensal microbiota which are not classically considered pathogenic can prompt and flare autoimmunity when fine regulation of immune tolerance does not work properly [2]. Not only were anti-Saccharomyces cerevisiae autoantibodies (ASCA) deemed to herald Crohn's disease even before clinical onset in slightly over 30% of patients [3, 4], but they were also recently tied to several other autoimmune diseases such as RA, SLE and APS compared to control subjects. What corroborates our findings on the immuno-pathogenetic role of *S. cerevisiae*, the current brewing and baking industry staple, is that cross-reactive epitopes on β2GPI and *S. cerevisiae* have been detected in ASCA-positive APS patients (20%) [5]. Indeed, several other overlaps in molecular sequence between yeast phosphopeptidomannan and

conserved protein domains of specific autoantigen in humans have been analysed and identified through the National Center for Biotechnology Information (NCBI) database [2].

Last but not least, *S. cerevisiae* has been seen to possibly "*adjuvate*" vaccines such as hepatitis B vaccination by stimulating the immune system as carefully described in the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [2, 6]. Therefore, although vaccines have definitively been a mainstay in preventing life-threatening diseases, further achievements in risk-free prophylaxis are currently needed.

Overall, this interesting experiment may have resulted in a microbiome competition model by which a rise in lactobacilli levels was in fact patent and could have been responsible for the referred EAE amelioration [1]. Indeed, systemic candidiasis by *C. albicans* has been found to induce high levels of ASCA as compared to controls both in rabbits and in humans [2].

References:

1. K. Takata, T. Tomita, T. Okuno, M. Kinoshita et al. Dietary Yeasts Reduce Inflammation in Central Nerve System via Microflora. Ann Clin Transl Neurol. 2015; 2: 56–66.
2. Rinaldi M, Perricone R, Blank M, Perricone C, et al. Anti-Saccharomyces cerevisiae Autoantibodies in Autoimmune Diseases: from Bread Baking to Autoimmunity. Clinical Rev Allergy Immunol. 2013;45:152-61.
3. Grotto I, Gilburd B, Balicer RD et al. Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease. Gut. 2005;54;1232-1236.
4. Laass MW, Roggenbuck D, Conrad K. Diagnosis and classification of Crohn's disease. Autoimmun Rev. 2014;13:467-71.

5. Krause I, Blank M, Cervera R, Font J, et al. Cross-reactive epitopes on beta2-glycoprotein-I and Saccharomyces cerevisiae in patients with the antiphospholipid syndrome. Ann N Y Acad Sci. 2007;1108:481-8.
6. Perricone C, Colafrancesco S, Shoenfeld Y. The hepatitis B vaccine and ASIA (autoimmune/inflammatory syndrome induced by adjuvants): Relationship with Saccharomyces cerevisiae. Case Rep Intern Med. 2014;1;166-7.