ABvac40 elicits a predominantly Th2 immune response that supports its excellent safety profile

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INTRODUCTION

The balance between Th1 (cell-mediated) and Th2 (humoral) immune pathways is a key factor in determining the safety of a vaccine.

AN1792, the first Alzheimer´s disease (AD) vaccine entered clinical trials, was terminated due to meningoencephalitis attributed to a cell-mediated immflamatory response [1,2].Subsequent to the experience gained from AN1792 vaccine, immunotherapies for AD that predominantly activate Th2 cells would be strongly recommended.

ABvac40, was designed as the first active immunotherapy against the C-terminal end of amyloid β 1-40 (Aβ40) in order to avoid antibody binding to the unprocessed amyloid precursor protein (APP) inserted in the cell membrane (Fig.1). This vaccine has shown a great safety and tolerability profile in a phase I clinical trial as well as in the preliminary data from a currently ongoing phase II clinical trial. Confirmation of a **Th2 biased immune response** would suggest that ABvac40 does not induce a proinflammatory response, in agreement with the safety results reported.

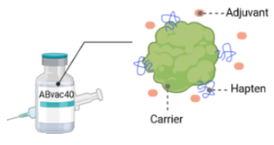

Figure 1. Schematic diagram of ABvac40 components.

OBJECTIVE

The aim of this study is to determine whether the **drug substance**, i.e., the hapten Aβ33–40 coupled to the carrier protein, induces a Th1 or Th2 polarized immune response in patients from phase II clinical trial AB1601, since aluminum hydroxide used as an adjuvant in ABvac40 is known to have a Th2-polarizing activity.

METHODS

Peripheral blood mononuclear cells (PBMCs) obtained from verum (n=37) and placebo (n=12) treated patients recruited to ABvac40 phase II study were stimulated *in vitro* by the drug substance of the vaccine.

The frequency of IFN-γ or IL-4-secreting T cells as prototypic Th1 and Th2 cytokines, respectively, were determined, at both the preimmune visit and after-five vaccine inoculations employing a commercially available IFN-γ/IL-4 dual FluoroSpot kit. A schematic illustration of the FluoroSpot assay steps is shown in Fig. 2.

All differences in spot forming units (SFUs) between groups were examined usign Mann Whitney test, except for preimmune versus after-five inoculations time points that were analyzed using Wilcoxon´s test.

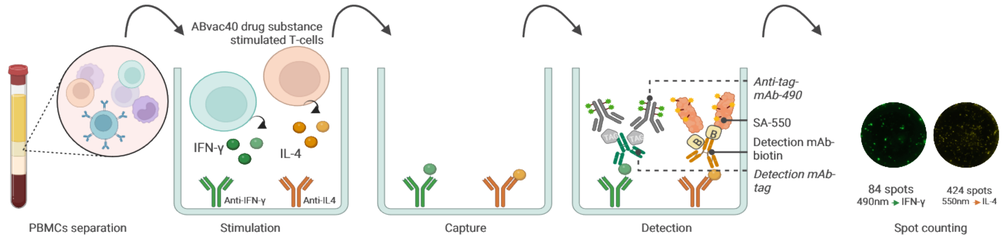

Figure 2. Schematic flowchart of FluoroSpot assay to detect the frequency of IFN-gamma and IL-4 secreting cells after stimulation with ABvac40 drug substance in patients from phase II clinical trial AB1601.

RESULTS

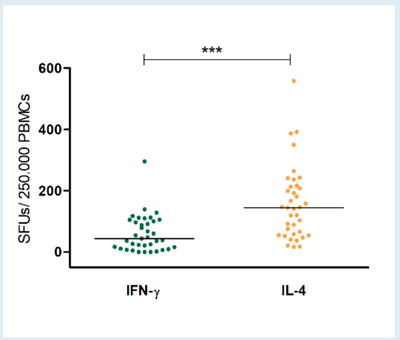

Figure 3. Scatter dot plot for IFN-γ (left) and IL-4 (right) from verum group samples. Circles represent verum group sample data, horizontal lines represent median values for each group.

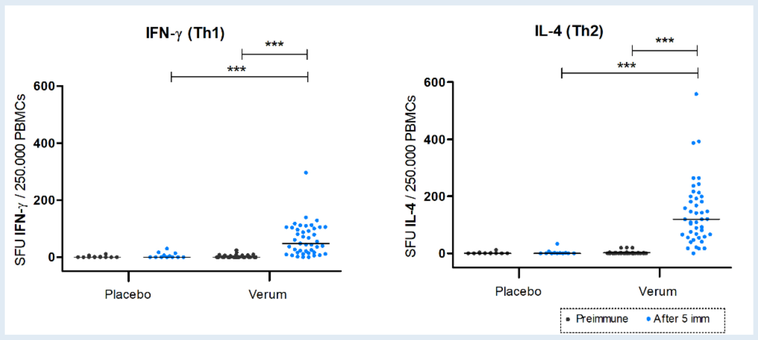

Figure 4. The frequency of PBMCs secreting IFN-γ (left) or IL-4 (right) after ABvac40 drug substance stimulation are compared between basal and after fice immunizations samples and between placebo and verum groups. Circles represent verum group sample data, horizontal lines represent median values for each group.

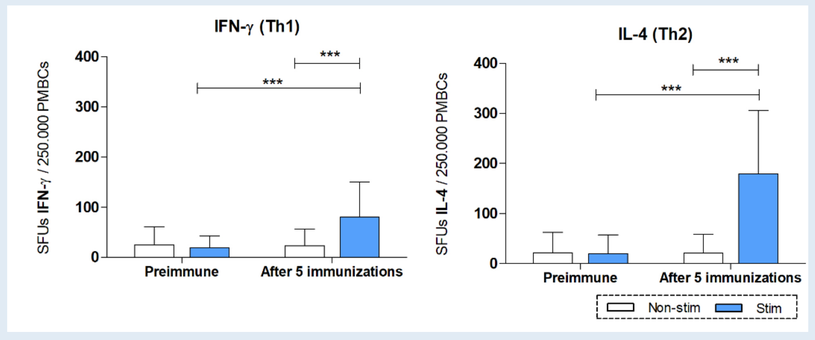

Figure 5. Mean SFUs (+ standard deviation) for IFN-γ (left) and IL-4 (right) responses before and after ABvac40 drug substance stimulation. Preimmune and after five ABvac40 doses samples from verum group were compared.

- A significantly **higher frequency of IL-4** SFUs was found in ABvac40 treated samples **compared to IFN-γ** (Fig. 3, $p < 0.0001$) while no placebo response was observed with any cytokine (Fig.4). To be noted that, among patients samples receiving ABvac40, 35 out of 37 developed a polarized Th2 response.
- The frequency of IFN-γ and IL-4 secreting cells **increased significantly after five immunizations** ($p < 0.0001$ in both cases) compared to the basal time point **in the verum group** (Fig.4). In the placebo samples, no significant changes were found in any case (data not shown).
- As expected, since the patients at the preimmune timepoint were not in contact with the vaccine, no significant changes between the stimulated and non-stimulated samples in the preimmune group were detected (Fig.4).
- Observed **SFUs were specific** to the cells stimulated by the **ABvac40 drug substance**, since in the verum group a significant increase of both cytokines was observed in response to ABvac40 stimulation (Fig.5, $p<0.0001$).

CONCLUSION

ABvac40 drug substance induces a **Th2 polarized T-helper immune response** that promotes a humoral response and minimizes a proinflammatory effect, which is consistent with the excellent safety profile shown by ABvac40 in phase I and phase II studies.

REFERENCES

(1) Pride M et al., Neurodegener Dis. 2008; 5(3-4):194-6.

(2) Mantile F and Prisco A. Biology (Basel). 2020 Nov 27;9(12):425.

Figures 1 and 2 y were generated by BioRender.