Dear Dr Fayad,

Following your demand, I read the article "*Anti-CD74 Autoantibodies in Axial SpondyloArthritis in a Population With Low HLA-B27 Prevalence*" published by "Frontiers in Immunology", and reviewed the original data and the exchanged emails between the authors you provided me.

There are two major points that raise important concerns in this publication regarding data Integrity.

From regulatory guidance's of the FDA and EMA (see links below): "Data Integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be Attributable, Legible, Contemporaneously recorded, Original or a true copy, and Accurate (ALCOA)."

https://www.fda.gov/media/119267/download

https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers

1. **Missing Data:**

There were a very large amount of missing data in the data sets you provided me, and reviewers did not raise this serious issue, as no mention of missing data was made in the manuscript. Missing data are numerous in the second measurements of both the donor and patient sets, as shown in the table below, which reflects the information you gave me:

Missing Data Summary	IgG4old	IgG4new	IgGAnew	IgA_IC
Donors Missing Samples/Total	2/102	61/102	62/102	35/102
% of Missing Data	2%	60%	61%	34%
Patients Missing Samples/Total	1/49	10/49	28/49	22/49
% of Missing Data	2%	20%	57%	45%

2. **Massaging IgG4 data:**

It seems that the second set of measurements had too many missing data, so that the authors used a mixture of the two sets of dosages for their analysis. This may be considered as not rigorous but is understandable. However, as correlations between results of the first and second sets of dosages appeared as very poor in the data you provided me, this should not have been done. The work does not follow regulatory guidance (see links below):

https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf

Furthermore, in available individual pairs of data, it seems that the authors arbitrarily chose one of the two data, to build the analysis sample as shown in the following examples, taken from the original Excel file you provided me:

Patient LB034:   IgG4old = 0.73   IgG4new = 3.99   IgG4Mixed = 3.99

Patient LB041: IgG4old = 0.13   IgG4new = 0.52   IgG4Mixed = 0.52

Patient LB045: IgG4old = 0.17   IgG4new = 0.56   IgG4Mixed = 0.56

Patient LB046: IgG4old = 0.38   IgG4new = 2.76   IgG4Mixed = 2.76

Patient LB048: IgG4old = 19.82   IgG4new = 2.42   IgG4Mixed = 2.42

Patient LB052: IgG4old = 0.12   IgG4new = 0.55   IgG4Mixed = 0.55

Patient LB053: IgG4old = 0.11   IgG4new = 0.59   IgG4Mixed = 0.59

Patient LB055: IgG4old = 0.11   IgG4new = 0.56   IgG4Mixed = 0.56

Patient LB059: IgG4old = 0.17   IgG4new = 0.54   IgG4Mixed = 0.54

Patient LB060: IgG4old = 0.13   IgG4new = 5.88   IgG4Mixed = 5.88

Donor LB127: IgG4old = 0.25   IgG4new = 0.93   IgG4Mixed = 0.25

Donor LB138: IgG4old = 0.36   IgG4new = 0.81   IgG4Mixed = 0.36

Donor LB144: IgG4old = 0.21   IgG4new = 1.33   IgG4Mixed = 0.21

Donor LB166: IgG4old = 0.25   IgG4new = 0.70   IgG4Mixed = 0.25

Donor LB171: IgG4old = 0.18   IgG4new = 0.98   IgG4Mixed = 0.18

Donor LB187: IgG4old = 0.15   IgG4new = 0.61   IgG4Mixed = 0.15

Donor LB202: IgG4old = 1.58   IgG4new = 0.81   IgG4Mixed = 0.81

Donor LB204: IgG4old = 0.25   IgG4new = 3.10   IgG4Mixed = 3.10

Donor LB208: IgG4old = 2.45   IgG4new = 0.59   IgG4Mixed = 0.59

No doubt that if the authors had picked the other value in these paired data for the analysis, results would have been different. As no mention was made in the authors' manuscript of these two sets of data you provided me, reviewers could not disclose the probable manipulation of data, and the manuscript, which is elegantly written, was accepted. I must say I am very glad not to see you among the authors of this article, given the hidden way the data were obtained. Results were not confirmed, as you know, by other teams who studied the relationship between Anti-CD74 antibodies and axial spondyloarthropathy.

In summary, there were gross mistakes in the building of the data set that was analyzed in this manuscript, that were hidden to the reviewers. This should lead your University to investigate in deep a potential forgery, which appears to me as probable, if the elements you gave me are true. These elements should then certainly be evaluated and taken into consideration.

Sincerely yours

Thomas Bardin

Emeritus Professor,

Paris Cité University, France