Reviewer's report

**Title:** Autoantibodies to Tumor Associated Antigens as Early Detection Biomarkers for Lung Cancer or Noncalcified Nodules

**Version:** 1 **Date:** 2 September 2009

**Reviewer:** Caroline Chapman

**Reviewer's report:**

All Major
1. Title - misleading and does not reflect the paper.
2. Abstract – There are words missing and the results stated do not agree with the results in the main body of the paper
3. Introduction is insufficiently referenced. The introduction also states results of a number of trails (without numbers, normals or relevance) - it is disorganised and unfocussed. They state NY-ESO abs found in 'few cancers' but only reference 1 paper and no number (not Sahin or Chapman). The authors talk a great deal about other cancers and far less about lung cancer – ie put id data that that is not relevant to this paper and leave out other.
   The authors talk at length about MUC1 but it not used in this study and should be removed
   The introduction needs serious restructuring and rewriting. The authors need to focus down on lung cancer and discuss the antigens used in the study.
4. Study Population:
   The normals tested were younger than the cancers - why? – no information was available and they were likely to be non smokers so not a suitable match. Why were these normals selected if such a large other group was available; they also need larger numbers.
5. 10% of the GGO were stated as having developed cancer – when? – did they have before and after bloods? Which samples were positive and which negative (results) Aabs have been described up to 5 years before the cancer- would be good to show if these patients had early aabs
6. No details on the lung cancers were given – stage, grade, treatment, type etc etc
   Ranges and SD of all ages need adding
7. Measurement of immunoreactivity: insufficient detail presented
7a What media and temperatures were the antigens grown at? Were they native preps/ denature / inclusion bodies. How pure? How was purity assessed?
7b What negative control protein and Positive control antibodies was used?
7c How many times were the samples assessed –
7d What was the reproducibility of the assay? How was it assessed
7e How was the cut off for positivity determined?
7f How can the authors be sure they were not measuring an age effect.
7g How can they vbe sure it was specific binding - were any blots performed?
7h 10% of the GGO developed cancer but the data on these was not shown or compared
Also those that resolved – the data should be shown
7i Are CT with no nodules normals – why therefore are the ages different
7j More samples are needed to be assessed to be sure of the results – the data shown was insufficiently analysed.
7k They need to show a plot of the logistic regression scores for each subject.
The also need to show individual sensitivities and specificities of each group as it is not clear from figure 1 how such good ROC curves can be produced.
7l The results state varying specificities – and it is hard to see how these were generated. Abstract results stated 24/26 healthy controls identified as non cancer – but state 97% specificity for cancer vs ….. word missing ( ) (this occurs more than once).
7m Results state 31/36 controls were correctly classified = 86% but then they state specificity of 97%! clearly this does not agree re a suitable robust test
8 Table 3 clearly states the test could distinguish between controls and no-nodules – but surely these are normal too
How can this be an accurate test if it can distinguish better between no nodules and normals than no nodules and cancer?
The box plots do not suggest such good specificity – or that such a test could work in another group
The abstract states the ROC curves were also based on age but this is not shown in table 4. Not all data is presented and it is unclear how such good sensitivity and specificity is acheived here, or could be achieved in future studies based on the results presented.
The paper should focus only on the title subject.
The paper needs to show all data.
The discussion does is not sufficient

Minor: Many abbreviations are not in presented full.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

Potentially Yes

I hold a consultancy for Oncimmune Ltd - a company involved in detection of cancer associated autoantibodies.