Reviewer's report

Title: ARG098, a novel anti-human Fas antibody, shows strong cytotoxic effects, suppresses synovial hyperplasia, and prevents cartilage destruction in rheumatoid arthritis.

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Reviewer: Juan D Canete

Reviewer's report:

- The authors of this long manuscript try to demonstrate that ARG098, a chimerical monoclonal Fas antibody, is a potential therapy for rheumatoid arthritis. Despite of the large experimental work performed by the authors, we have several important concerns regarding accuracy of conclusions of this study.

Major points:

- The title is something misleading because the work is not performed in either a true experimental model of RA not in RA patients. The authors should discuss why is not possible to study this drug in a mouse transgenic for human-Fas (Fas-KO mouse exist).

- From these Results it is not clear the mechanism of action of ARG098 because the authors do not detect a clear increase in apoptosis. Probably they should use control positive apoptotic cells induced by Fas-ligand in order to confirm if they can detect apoptosis or they have problems with apoptotic signaling in their cells. Similarly, the lack of effects of this drugs on PBMC, hepatocytes and condrocytes/cartilage is intriguing and remains to be well explained and more experiment are needed before to conclude that this drug has no toxic effects on these cells. Indeed the lack of toxic effects of this drug should be demonstrate at the systemic level (animal model).

As ARG098 is a IgM monoclonal antibody and IgM can activate the complement system, it would be interesting to role out that activation of complement is implicated in the cytotoxic effects of this drug.

Abstract should be largely reduced and strong statements on the anti-RA effect of this drug should be modified or eliminated.

Background is too long and contains paragraphs on treatment of RA which no reflect the current approach to the therapy of RA (prosthesis and synovectomy are every time less performed in RA management). This introduction needs be re-written more concisely and more focused on the relevance of the target and in the rationale of the study (including possible undesirable effects of anti-Fas).

Discussion is also is very long and little focused in the real translational relevance of their findings. It should include limitations of the study as well as
future research needed to propose this drug as potential therapy for RA (Surprisingly we read in Conclusion that this drug is now in Phase I/II clinical trials).

Minor points:

- Methods and Results should be reduced or some part of them (some figures) could be included as supplemental material).

- There is redundancy and a lot of spelling mistakes throughout all the manuscript and therefore it should be revised in deep by an expert English writer.

- In pag. 20, last paragraph, the authors state "synovium infiltrating lymphocytes.... consisting of T cells, B cells, macrophages and neutrophils and these lymphocytes..." Please modify.

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

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests