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.

Version: 2 Date: 22 June 2010

Reviewer: Paul-Peter Tak

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Major Compulsory Revisions:

1) Original comment: The authors report the superior effect of of ARG098 in inducing apoptosis in Jurkat cells and RA FLS compared to historical attempts. To make this claim, the authors need to show ARG098 side by side with another anti-Fas antibody such as CH-11. In particular, they should examine dose responses of another Fas antibody in Jurkat cells, and find concentrations of this antibody and ARG098 which induce comparable levels of apoptosis in Jurkat. Then, the two antibodies should be compared at these concentrations in RA FLS. Only then can the authors claim any superiority of the ARG098 compound.

Evaluation: the authors mention only unpublished data regarding relative efficacies of ARG098, 7C11, and CH-11 in the induction of RA FLS apoptosis. Given that a critical element of their manuscript is that ARG098 is an improvement upon other anti-Fas antibodies, it is unclear to me why this data isn’t shown in the manuscript. It is also unclear from their remark if the antibodies were studied in parallel in the same RA FLS cell lines. Finally, the 7C11-induced apoptosis they report as data not shown is 70% of that achieved by ARG098, suggesting little eventual improvement in efficacy in vivo. Again, it would have been helpful if the authors had attempted to compare these antibodies in vivo as well. The authors continue to make strong unsubstantiated claims in the abstract and conclusion (“These results suggest that ARG098 is a novel and efficacious for RA treatment”).

2) Original comment: While the authors attribute the historical lack of efficacy of anti-Fas antibodies on RA FLS to, among other things, their need for multimerization, a very good recent study by Pundt and colleagues (Arthritis Res Ther, 2009, 11/1/R16) demonstrated that RA FLS susceptibility to FasL-induced death was exquisitely dependent upon the proliferation rate of cells in vitro, as well as cell cycling status and culture confluency. The authors need to take into consideration that their positive results with ARG098 are secondary to tissue culture conditions –eg., there is no evidence in the methods section that they serum-starve their FLS or achieve cell cycle arrest.

Evaluation: The authors respond that they performed all of their experiments in cells cultured in 10% FBS. Pundt and colleagues have reported that proliferating
FLS are least susceptible to FasL-induced apoptosis. Again, testing other anti-Fas antibodies or soluble FasL would have been helpful to the authors to allow us to draw some intrinsic data relative to published literature. Inclusion of 10% FBS in the medium will also mask intrinsic, imprinted properties of RA FLS, as demonstrated by Buckley and colleagues at the level of gene expression.

3) Original comment: The authors ignore a number of important manuscripts published on this topic such as effects of PI3 kinase signaling in RA FLS resistance to Fas-dependent apoptosis from the group of Pope, and others. Additionally, they fail to examine the effect of their antibody on synovial macrophages, an important synovial population reported to be resistant.

Evaluation: The authors still have macrophages and dendritic cells in their culture after 5 passages, or are using mixed cell populations in early cultures??!! In this case, we don’t know what cell population we are studying, and it is even more difficult to extrapolate in vitro results to their in vivo results.

4) Both introduction and discussion sections are unnecessarily long, a result of inadequate organization and internal redundancies – both sections could be shortened by 33-50%.

Evaluation: The authors have shortened both sections sufficiently in length, but organization within each section is still poor.

5) Extreme care should be given to grammatical errors appearing throughout the manuscript.

Evaluation: The authors have greatly improved grammar throughout the manuscript but the manuscript will still require the firm hand of the editorial office.

Level of interest: An article of limited interest

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

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.